Table 3 Sedation treatments used during acute management

	Total (n = 83)	Group 1 (n = 7)	Group 2 (n = 14)	Group 3 (n = 62)	P-value
Analgesia/sedative agents					0.842
Yes	82 (98.8%)	7 (100%)	14 (100%)	61 (98.4%)	
No	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	
Muscle relaxant					0.373
Yes	72 (86.7%)	7 (100%)	13 (92.9%)	52 (83.9%)	
No	1 (13.3%)	0 (0.0%)	1 (7.1%)	10 (16.1%)	
Degree of sedation level					0.752
Movability acceptable	30 (36.1%)	3 (42.9%)	5 (35.7%)	22 (35.4%)	
Movability unacceptable	48 (57.8%)	4 (57.1%)	9 (64.3%)	35 (56.5%)	
Other	5 (6.0%)	0 (0.0%)	0 (0.0%)	5 (8.1%)	
Mode of muscle relaxant administration					0.797
Administration as necessary	17 (23.6%)	2 (28.6%)	4 (30.8%)	11 (21.2%)	
Continuous infusion	52 (72.2%)	5 (71.4%)	9 (69.2%)	38 (73.1%)	
Other	3 (4.2%)	0 (0.0%)	0 (0.0%)	3 (5.7%)	

those with isolated CDH with a prenatal diagnosis, the overall survival rate was 79.3%. The survival rates of isolated CDH with a prenatal diagnosis in G1, G2, and G3 were 87.2%, 75.2%, and 74.3%, respectively. The survival rate in G1 was significantly higher than that in G2 or G3 (G1 vs G2, P = 0.013; OR: 0.447 [95%CI: 0.236–0.847], G1 vs G3, P = 0.007; OR: 0.425 [95%CI: 0.230–0.787]).

Delivery mode

There were no differences in policies regarding the delivery mode used among the three groups. An elective cesarean section was the first-line treatment at almost all of the hospitals (G1, 42.9%; G2, 71.4%; G3, 71.0%; P = 0.535).

Ventilator strategies

HFOV was widely used and the infants were managed in accordance with the policy of gentle ventilation with permissive hypercapnia in most of the hospitals in G1, G2, and G3. Overall, there was variability in the tolerable levels of blood gas parameters. There were no differences in the tolerable level of blood gas parameters among the three groups. The highest percentage for the tolerable levels of preductal $PaCO_2$, preductal PaO_2, preductal SpO_2, and preductal pH were as follows: 50–60 mmHg, 60–70 mmHg, 90–95%, and 7.30–7.35, respectively (Table 2).

Sedation

In most of the hospitals in G1, G2, and G3, analgesia, sedative agents, and muscle relaxants were widely used. In approximately half of all the hospitals, the infants with CDH were cared for without body movements. Muscle relaxants were administered by continuous infusion in most of the hospitals. The strategies of sedation were the same among the three groups (Table 3).

Specific treatments of PPHN

Most of the hospitals in Japan were able to treat infants with PPHN using iNO, independent of hospital volume (G1, 100%; G2, 100%; G3, 90.3%; P = 0.901). On the other hand, ECMO tended to be available only in the high-volume hospitals (G1, 85.7%; G2, 78.6%; G3, 46.8%; P = 0.073).

Timing of surgical repair

The timing of surgical closure of the diaphragmatic defect was not different among the groups. In most of the hospitals, surgery was performed after stabilization of the respiratory and circulatory conditions. Regarding the postnatal day of surgical repair, surgery was performed within 4 postnatal days in most of the hospitals. In almost all of the hospitals in G1, surgery was performed within 2 postnatal days (Table 4).

Table 4 Timing of surgical repair

	Total (n = 83)	Group 1 (n = 7)	Group 2 (n = 14)	Group 3 (n = 62)	P-value
Timing of surgical repair					0.818
Early operation	4 (4.8%)	1 (14.3%)	0 (0.0%)	3 (4.8%)	
Decision depending on the situation	34 (41.0%)	4 (57.1%)	5 (35.7%)	25 (40.3%)	
After stabilization	41 (49.4%)	2 (28.6%)	8 (57.1%)	31 (50.0%)	
No treatment principle	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	
No response	3 (3.6%)	0 (0.0%)	1 (7.1%)	2 (3.2%)	
Postnatal day of surgical repair					0.139
Day 0	2 (2.4%)	1 (14.3%)	0 (0.0%)	1 (1.6%)	
Day 1–2	31 (37.3%)	4 (57.1%)	5 (35.7%)	22 (35.5%)	
Day 3–4	37 (44.6%)	1 (14.3%)	6 (42.9%)	30 (48.4%)	
Day 5–7	5 (6.0%)	1 (14.3%)	0 (0.0%)	4 (6.5%)	
Day 8–	1 (1.2%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	
No response	7 (8.4%)	0 (0.0%)	2 (14.3%)	5 (8.1%)	

Difference in strategies by physicians of different specialties

In 54 institutes, neonatologists treat CDH infants. In five institutes, pediatric surgeons collaborate with neonatologists. Therefore, neonatologists were involved in CDH treatments in 59 institutes. On the other hand, in 24 institutes, the attending doctors did not belong to the department of neonatology. The attending physicians were pediatric surgeons, pediatric cardiologists, anesthesiologists, obstetricians and from other specialties. The strategies of CDH treatments employed by neonatologists versus non-neonatologists (data not shown) were not different. The survival rates for the infants treated by neonatologists versus those treated by non-neonatologists (74.8% vs 74.0%; $P = 0.87$) were not different.

Discussion

This study is the first Japanese nationwide survey of infants with CDH and demonstrates the current state of CDH care in Japan. The overall survival rate of all cases was 74.5%. The survival rate of cases with a postnatal diagnosis was significantly higher than that of cases with a prenatal diagnosis. The survival rate of cases with a prenatal diagnosis was dependent on hospital volume. In particular, the survival rate of isolated cases with a prenatal diagnosis in G1 was significantly higher than that in G2 or G3.

A systematic review of CDH, which included 763 patients from 13 reports, showed that the overall survival rate and the survival rate of infants with isolated CDH were 79% (range: 69–93%) and 85% (range: 78–96%), respectively.[6] In this study, the overall survival rate and the survival rate of infants with isolated CDH were 74.5% and 82.7%, respectively. The survival rate of CDH infants in Japan was compatible with that of other countries. Focusing on the cases with a prenatal diagnosis, both the overall survival rate and the isolated CDH survival rate were significantly associated with the hospital volume in this study. The dependency of the survival rates on the hospital volume was not clear. One possibility is the habituation to care for critical newborns. The care and handling of critical patients are very important factors in neonatal medicine and they might affect the patients' outcome. The infants with CDH, especially prenatally diagnosed cases, are critical and can easily develop into PPHN. The medical staff members in large-volume hospitals (G1) are generally used to dealing with CDH. This might be the reason for the low mortality of isolated CDH with a prenatal diagnosis in G1. The prenatal diagnosis makes it possible to plan the optimal time and place of delivery. Neonatal transport is associated with an increased mortality.[7] Therefore, in order to increase the survival rates, maternal cases with a prenatal diagnosis should be referred to tertiary centers.

In prenatally diagnosed CDH, the best delivery mode remains unknown. While the delivery mode is not associated with the outcome of prenatally diagnosed CDH,[8] recent data suggest that cesarean sections increase survival rates[9] or increase survival without ECMO.[10] In Japan, elective cesarean sections were the first-line choice in most of the hospitals. The reason for this might be that the number of medical staff was not adequate to care for such critical patients on holidays and/or night shifts.

The most important ventilator strategy for treating CDH is avoiding ventilator-induced lung injury (VILI). To avoid and minimize VILI, gentle ventilation with permissive hypercapnia[11,12] and early conversion to HFOV have been used.[13,14] Although the majority of Japanese hospitals applied gentle ventilation with permissive hypercapnia, the tolerable levels of blood gas parameters varied widely. In actuality, infants with CDH were not always treated with gentle ventilation. Originally, the gentle ventilation strategy reported by Wung included the use of respiratory treatments without muscular relaxants, as well as the use of permissive hypercapnia.[12] The systematic review revealed that the infants with CDH received light sedation, and muscle relaxants tended to be used less frequently.[6] In our study, both analgesia and muscle relaxants were widely used in most of the hospitals. A pulmonary hypertensive crisis can be triggered by handling the infants or from nursing care provided at bedside. To prevent pulmonary vasospasms secondary to these procedures, most Japanese neonatologists/pediatric surgeons might therefore choose to keep such patients paralyzed using analgesia and muscle relaxants.

Most infants with CDH suffer from PPHN. iNO is one of the treatments used for severe respiratory failure and/or PPHN. Although there is little evidence for the effectiveness of iNO for CDH, iNO has nevertheless been widely used to treat CDH infants.[15,16] In this study, iNO was found to be widely available in Japanese neonatal intensive care units. One report from Japan showed that the combination of iNO and early operations improved the outcome and reduced the need for ECMO.[17] With the widespread dissemination of gentle ventilation techniques, the use of ECMO has decreased in some centers.[14] ECMO was used in only 7.4% of CDH infants in a Canadian study.[18] Although treatment with iNO and HFOV reduced the need for ECMO, it did not reduce mortality in infants with PPHN.[19] The systematic review showed that preoperative mortalities were reduced in ECMO centers.[1] The Congenital Diaphragmatic Hernia Study Group demonstrated that ECMO significantly improved survival rates in CDH neonates with a high risk of mortality.[20] In this study, ECMO tended to be more available in the hospitals in G1; however, a statistically significant difference was not seen ($P = 0.073$). In order to treat infants with critical CDH, ECMO should therefore be provided in tertiary centers.

In about half of the hospitals that participated in this study, infants with CDH were operated on after stabilization. The role of the timing of surgery in influencing outcomes of CDH is widely debated and the published reports provide controversial results. Some centers delay surgery until physiologic stabilization has occurred, while others prefer to perform surgery immediately after birth.[21] Rozmariek proposed that the outcome of patients with CDH depends more on the degree of physiologic derangement than on the timing of surgery.[22] Sometimes surgery might worsen or trigger bouts of PPHN. The optimization of hemodynamic and respiratory parameters might improve the outcome.

Some centers described their protocols for treating CDH and the possible beneficial effects of these protocols.[23–25] In these studies, the outcome for infants who received standardized

treatment was favorable compared with that for infants who did not receive standardized treatment. In our study, the ventilation strategies, such as the use of tolerable levels of blood gas parameters, used among the centers varied widely. Multicenter collaboration and the establishment of successful protocols are essential for improving outcomes in patients with CDH.[26]

A few reports have demonstrated the existence of a hospital-volume–patient-outcome correlation for CDH.[4,27] The Canadian Pediatric Surgery Network reported a volume–outcome correlation for infants with CDH. They classified hospitals into high-volume (≥12 cases/22 months) and low-volume (<12 cases/22 months) groups according to the number of patients treated. The high-volume hospitals had a significantly higher survival rate (90% vs 77%).[27] A recent study using the Pediatric Health Information System in the USA reported a correlation between hospital volume and outcome. In their study, 2203 infants with CDH from 37 children's hospitals were divided into three groups according to the number of CDH cases at each individual hospital.[4] Hospital volume was categorized as being low (≤6 cases/year), medium (6–10 cases/year), or high (≥10 cases/year). The results showed that the high-volume and medium-volume centers had significantly lower mortality rates compared with the low-volume centers. In this study, we divided hospitals into three groups according to the number of patients treated. There are too many hospitals in Japan to centralize infants with CDH. Even in G1, the median (range) number of patients was 29 (22–43) during 5 years. Although individual hospitals had a small number of CDH infants, the survival rate of the infants with prenatally diagnosed CDH was dependent on hospital volume. Therefore, we suggest that, at a minimum, the cases with a prenatal diagnosis should be referred to tertiary centers.

This study employed a retrospective survey using a questionnaire and was not designed to compare the outcomes that resulted from the management strategies. Judging from the birth prevalence of CDH,[1–3] the number of patients in our survey corresponded to approximately half of the estimated cases for that period. Consequently, the results of this study accurately describe the current status of infants with CDH in Japan. This study will therefore provide useful information for prenatal counseling of parents and for cross-national research.

The perinatal management strategies used to treat CDH were the same for the three groups of institutions divided based on the number of cases treated. The survival rate was dependent on hospital volume, particularly in cases with a prenatal diagnosis. We concluded that it might be important to centralize the infants with CDH in tertiary centers in Japan in order to improve survival rates.

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References

1 Beresford MW, Shaw NJ. Outcome of congenital diaphragmatic hernia. *Pediatr. Pulmonol.* 2000; **30**: 249–56.
2 de Buys Roessingh AS, Dinh-Xuan AT. Congenital diaphragmatic hernia: current status and review of the literature. *Eur. J. Pediatr.* 2009; **168**: 393–406.
3 Langham MR Jr, Kays DW, Ledbetter DJ, Frentzen B, Sanford LL, Richards DS. Congenital diaphragmatic hernia. Epidemiology and outcome. *Clin. Perinatol.* 1996; **23**: 671–88.
4 Bucher BT, Guth RM, Saito JM, Najaf T, Warner BW. Impact of hospital volume on in-hospital mortality of infants undergoing repair of congenital diaphragmatic hernia. *Ann. Surg.* 2010; **252**: 635–42.
5 Chung JH, Phibbs CS, Boscardin WJ, Kominski GF, Ortega AN, Needleman J. The effect of neonatal intensive care level and hospital volume on mortality of very low birth weight infants. *Med. Care* 2010; **48**: 635–44.
6 Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. *J. Perinatol.* 2007; **27**: 535–49.
7 Aly H, Bianco-Batlles D, Mohamed MA, Hammad TA. Mortality in infants with congenital diaphragmatic hernia: a study of the United States National Database. *J. Perinatol.* 2010; **30**: 553–7.
8 Safavi A, Lin Y, Skarsgard ED. Perinatal management of congenital diaphragmatic hernia: when and how should babies be delivered? Results from the Canadian Pediatric Surgery Network. *J. Pediatr. Surg.* 2010; **45**: 2334–9.
9 Harmath A, Hajdu J, Hauzman E, Pete B, Rona Z, Papp Z. Experiences in the perinatal management of congenital diaphragmatic hernia during the last 15 years in a tertiary referral institute. *Fetal Diagn. Ther.* 2007; **22**: 209–16.
10 Frenckner BP, Lally PA, Hintz SR, Lally KP. Prenatal diagnosis of congenital diaphragmatic hernia: how should the babies be delivered? *J. Pediatr. Surg.* 2007; **42**: 1533–8.
11 Logan JW, Cotten CM, Goldberg RN, Clark RH. Mechanical ventilation strategies in the management of congenital diaphragmatic hernia. *Semin. Pediatr. Surg.* 2007; **16**: 115–25.
12 Wung JT, Sahni R, Moffitt ST, Lipsitz E, Stolar CJ. Congenital diaphragmatic hernia: survival treated with very delayed surgery, spontaneous respiration, and no chest tube. *J. Pediatr. Surg.* 1995; **30**: 406–9.
13 Downard CD, Jaksic T, Garza JJ *et al.* Analysis of an improved survival rate for congenital diaphragmatic hernia. *J. Pediatr. Surg.* 2003; **38**: 729–32.
14 Bohn D. Congenital diaphragmatic hernia. *Am. J. Respir. Crit. Care Med.* 2002; **166**: 911–5.
15 The Congenital Diaphragmatic Hernia Study Group. Treatment evolution in high-risk congenital diaphragmatic hernia: ten years' experience with diaphragmatic agenesis. *Ann. Surg.* 2006; **244**: 505–13.
16 Skari H, Bjornland K, Frenckner B *et al.* Congenital diaphragmatic hernia: a survey of practice in Scandinavia. *Pediatr. Surg. Int.* 2004; **20**: 309–13.
17 Okuyama H, Kubota A, Oue T *et al.* Inhaled nitric oxide with early surgery improves the outcome of antenatally diagnosed congenital diaphragmatic hernia. *J. Pediatr. Surg.* 2002; **37**: 1188–90.
18 Baird R, Eeson G, Safavi A, Puligandla P, Laberge JM, Skarsgard ED. Institutional practice and outcome variation in the management of congenital diaphragmatic hernia and gastroschisis in Canada: a report from the Canadian Pediatric Surgery Network. *J. Pediatr. Surg.* 2011; **46**: 801–7.
19 Fliman PJ, deRegnier RA, Kinsella JP, Reynolds M, Rankin LL, Steinhorn RH. Neonatal extracorporeal life support: impact of new therapies on survival. *J. Pediatr.* 2006; **148**: 595–9.
20 The Congenital Diaphragmatic Hernia Study Group. Does extracorporeal membrane oxygenation improve survival in neonates with congenital diaphragmatic hernia? The Congenital Diaphragmatic Hernia Study Group. *J. Pediatr. Surg.* 1999; **34**: 720–4. discussion 24–5.

21 de la Hunt MN, Madden N, Scott JE *et al.* Is delayed surgery really better for congenital diaphragmatic hernia?: a prospective randomized clinical trial. *J. Pediatr. Surg.* 1996; **31**: 1554–6.
22 Rozmiarek A, Qureshi F, Cassidy L, Ford H, Hackam D. Factors influencing survival in newborns with congenital diaphragmatic hernia: the relative role of timing of surgery. *J. Pediatr. Surg.* 2004; **39**: 821–24.
23 Tracy ET, Mears SE, Smith PB *et al.* Protocolized approach to the management of congenital diaphragmatic hernia: benefits of reducing variability in care. *J. Pediatr. Surg.* 2010; **45**: 1343–8.
24 Antonoff MB, Hustead VA, Groth SS, Schmeling DJ. Protocolized management of infants with congenital diaphragmatic hernia: effect on survival. *J. Pediatr. Surg.* 2011; **46**: 39–46.
25 van den Hout L, Schaible T, Cohen-Overbeek TE *et al.* Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. *Fetal Diagn. Ther.* 2011; **29**: 55–63.
26 van den Hout L, Sluiter I, Gischler S *et al.* Can we improve outcome of congenital diaphragmatic hernia? *Pediatr. Surg. Int.* 2009; **25**: 733–43.
27 Javid PJ, Jaksic T, Skarsgard ED, Lee S. Survival rate in congenital diaphragmatic hernia: the experience of the Canadian Neonatal Network. *J. Pediatr. Surg.* 2004; **39**: 657–60.

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Original Article

Prognostic factors of congenital diaphragmatic hernia accompanied by cardiovascular malformation

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Abstract ***Background***: Congenital diaphragmatic hernia is associated with cardiovascular malformation. Many prognostic factors have been identified for isolated congenital diaphragmatic hernia; however, reports of concurrent congenital diaphragmatic hernia and cardiovascular malformation in infants are limited. This study evaluated congenital diaphragmatic hernia associated with cardiovascular malformation in infants. Factors associated with prognosis for patients were also identified.

Methods: This retrospective cohort study was based on a Japanese survey of congenital diaphragmatic hernia patients between 2006 and 2010. Frequency and outcome of cardiovascular malformation among infants with congenital diaphragmatic hernia were examined. Severity of congenital diaphragmatic hernia and cardiovascular malformation were compared as predictors of mortality and morbidity.

Results: Cardiovascular malformation was identified in 76 (12.3%) of 614 infants with congenital diaphragmatic hernia. Mild cardiovascular malformation was detected in 19 (33.9%) and severe cardiovascular malformation in 37 (66.1%). Their overall survival rate at discharge was 46.4%, and the survival rate without morbidity was 23.2%. Mortality and morbidity at discharge were more strongly associated with severity of cardiovascular malformation (adjusted OR 7.69, 95%CI 1.96–30.27; adjusted OR 7.93, 95%CI 1.76–35.79, respectively) than with severity of congenital diaphragmatic hernia.

Conclusions: The prognosis for infants with both congenital diaphragmatic hernia and cardiovascular malformation remains poor. Severity of cardiovascular malformation is a more important predictive factor for mortality and morbidity than severity of congenital diaphragmatic hernia.

Key words cardiac anomaly, diaphragmatic hernia, liver herniation, prognostic factor.

In recent years, outcomes in patients with isolated congenital diaphragmatic hernia (CDH) have markedly improved because of advances in perinatal management. Some studies have reported overall survival and intact survival rates exceeding 80% and 60%, respectively.[1–3] However, CDH is also known to be associated with other congenital malformations. Cardiovascular malformation (CVM) is found in 10–20% of infants with CDH.[4,5] Some reports have shown higher mortality rates in infants with both CDH and CVM than in those with CDH alone.[6,7]

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Many prognostic factors, such as liver herniation, lung-to-head ratio, Apgar score, and pulmonary artery size, have been previously evaluated for their association with isolated CDH. These factors are important for counseling of parents or management in the perinatal period.[8–12] However, in infants with both CDH and CVM, the association of the severity of these conditions with mortality and morbidity remains uncertain. This study evaluated the incidence and outcome of CDH associated with CVM and factors influencing the prognosis for infants with CDH and CVM were also examined.

Methods

This study was approved by the ethics committees of the National Center for Child Health and Development, Nagoya University Hospital, Osaka University Graduate School of Medicine, Hyogo College of Medicine, Osaka Medical Center and Research

Institute for Maternal and Child Health, Osaka University Hospital and Graduate School of Medical Sciences, and Kyushu University. A questionnaire was distributed to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals. The survey inquired about infants with CDH born between 2006 and 2010. Of the 159 institutes invited to participate, 109 (68.8%) responded to the questionnaire. Of these, 26 institutes reported no CDH cases and 11 refused to participate in the survey, although some cases of CDH were treated at these institutes. Thus, the final sample included 72 institutes in which 614 CDH cases were treated during the study period.

Data from the CDH survey were combined with data from a nationwide survey conducted in Japan. All infants described as having cardiac defects were selected for review. Infants with patent foramen ovale, atrial septal defects, patent ductus arteriosus, and hemodynamically insignificant vascular malformation (including right aortic arch) were excluded from the review. The incidence of CVM among infants with CDH identified in the hospital survey was examined.

Factors influencing mortality and morbidity in infants with both CDH and CVM were assessed using multivariate analysis. Infants with trisomy 13 or trisomy 18 and those who received palliative care after birth were excluded from the analysis of prognostic factors. Severe CVM was defined as hemodynamically significant heart disease requiring surgical intervention. Severe CDH was defined as liver herniation. In infants with more than two CVM, the anomaly most likely to affect outcome was adopted. In addition, survival without morbidity was defined as no need for respiratory support, including oxygen supplementation, tube feeding, parenteral nutritional support, or vasodilation.[3]

All data were analyzed using the statistical software program Stat Flex for Windows version 6.0 (Artec, Osaka, Japan). Univariate analysis was performed to identify differences between survivors and non-survivors and differences between infants with and without morbidity at discharge or death. The χ^2-test, Fisher's exact test, the 2-sample test, and the Mann–Whitney nonparametric test were selected as appropriate. Multiple logistic regression analysis was performed to evaluate the association of CDH and CVM severity with mortality and morbidity. Mortality was defined as death during hospitalization. Statistical significance was set at $P < 0.05$.

Results

CVM was identified in 76 of the 614 (12.3%) infants. Life-limiting genetic defects were identified in 14 infants (trisomy 13, $n = 4$; trisomy 18, $n = 10$). Palliative care for severe CVM, trisomy 21, heterotaxia, or tracheal stenosis was administered in six cases, and full intervention was required in 56 cases. Mild CVM was detected in 19 (33.9%) of these 56 infants and severe CVM in 37 (66.1%) (Fig. 1).

Details of the 76 infants with CVM are provided in Table 1. Ventricular septal defect (VSD) was identified in four of the infants with trisomy 13 or trisomy 18, three infants with tetralogy of Fallot (TOF) and double-outlet right ventricle (DORV) with right ventricular outflow tract obstruction (RVOTO), and four

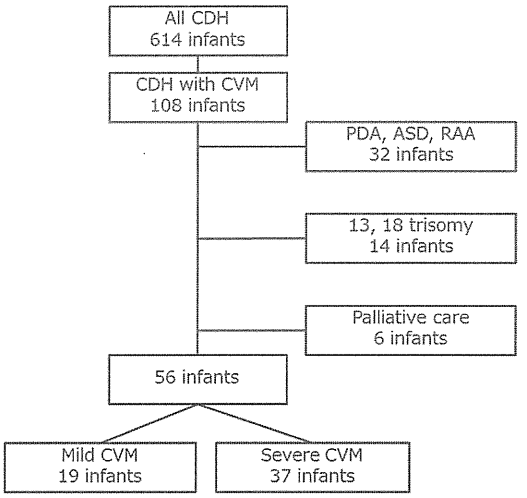

Fig. 1 Diagram summarizing the study population. ASD, atrial septal defect; CHD, congenital diaphragmatic hernia; CVM, cardiovascular malformation; PDA, patent ductus arteriosus; RAA, right aortic arch.

infants with DORV without RVOTO. The majority of infants with mild CVM had VSD ($n = 14$, 73.7%).

The overall survival rate at discharge of the infants with CVM who required full intervention was 46.4% (26/56). This rate for those with mild CVM and severe CVM was 77.8% (14/18) and 31.6% (12/38), respectively. The overall usage rate of extracorporeal membrane oxygenation (ECMO) and nitric oxide inhalation (iNO) were 8.9% (5/56) and 71.4% (40/56), respectively. On the other hand, the overall survival rate without morbidity at discharge was 23.2% (13/56). For those with mild and severe CVM, this rate was 50.0% (9/18) and 10.5% (4/38), respectively. Morbidities at discharge included use of supplemental oxygen ($n = 10$), tube feeding ($n = 6$), and vasodilation ($n = 4$). No ventilation, tracheostomy, or total parenteral nutrition was required at discharge for any of the patients.

Univariate analysis revealed that severe CVM was found significantly more frequently in non-survivors than in survivors (86.7% vs 46.2%, $P = 0.001$). However, no significant difference between survivors and non-survivors was observed for the other variables (including liver herniation, which was used to represent severity of CDH) (Table 2). Severe CVM was significantly more frequent in infants with morbidity at discharge or in non-survivors than in survivors without morbidity at discharge (79.1% vs 30.8%, $P = 0.001$) (Table 3). The adjusted OR for mortality in infants with CDH associated with CVM was 7.69 (95%CI 2.00–30.27) for infants with severe CVM and 0.49 (95%CI 0.12–1.91) for those with liver herniation. Morbidity in infants with CDH associated with CVM was calculated as 7.93 (95%CI 1.76–35.79) for those with severe CVM and 0.82 (95%CI 0.15–4.63) for those with liver herniation (Table 4).

In a subgroup analysis, the survival rate of infants with VSD was 72.2% (13/18); however, that of infants with the other CVM was <50%. No infants with hypoplastic left heart syndrome (HLHS) survived. In contrast, the intact survival rate in infants

Table 1 Types of cardiac defects observed in patients with CDH and CVM

n	13, 18 trisomy	Palliative care	Full intervention		Overall CVM
			Severe CVM	Mild CVM	
	14	6	37	19	76
VSD	4	2	5	14	25 (32.9%)
TOF or DORV with RVOTO	3	–	8	1	12 (15.8%)
DORV without RVOTO	4	–	4	–	8 (10.5%)
CoA or IAA	1	–	4	3	8 (10.5%)
HLHS	–	1	6	–	7 (9.2%)
SV	1	2	4		7 (9.2%)
PS or PA	–	–	1	1	2 (2.6%)
AVSD	1	–	1	–	2 (2.6%)
TAPVR	–	–	1	–	1 (1.3%)
TGA	–	–	1	–	1 (1.3%)
Truncus arteriosus	–	1	–	–	1 (1.3%)
TA	–	–	1	–	1 (1.3%)
TV dysplasia	–	–	1	–	1 (1.3%)

AVSD, atrioventricular septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; CVM, cardiovascular malformation; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interruption of the aortic arch; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricular tract obstruction; SV, single ventricle; TA, tricuspid valve atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

with VSD was 38.9% (7/18). The intact survival rate in infants with other CVM was very low (Table 5).

Discussion

Results of this report showed that CVM was concurrent with CDH in 12% of infants included in this study during this period. Ninety percent of infants with CVM (except those with trisomy 13 and trisomy 18) underwent full intervention. Despite this intervention, overall and intact survival rates at discharge were extremely poor (46% and 23%, respectively). VSD was the most common cardiac defect, and left-sided heart disease and conotruncal anomalies, such as TOF and DORV, were also common. Severe CVM was more closely associated with mortality and morbidity at discharge than liver herniation, which represented severe CDH in this study. The survival rate of infants with VSD was about 70%; however, less than 50% of infants with other types of CVM survived. In addition, even infants with VSD had low intact survival rate.

Table 2 Clinical characteristics of survivors and non-survivors. Data are presented as mean values ± SD or median values and (Q1–Q3)

Variables	Survivors	Non-survivors	*P*
Number of infants	26	30	
GA (wk)	37.7 ± 2.0	36.9 ± 2.9	0.254
BW(g)	2259 ± 517	2447 ± 623	0.229
Apgar score at 1 min	3 (2–5)	3 (2–4)	0.172
Apgar score at 5 min	5 (3–6)	5 (3–6)	0.418
Female	13 (50.0%)	17 (56.7%)	0.618
Vaginal delivery	6 (23.1%)	4 (13.3%)	0.738
Prenatal diagnosis	20 (76.9%)	25 (83.3%)	0.547
CDH left	24 (92.3%)	27 (90.0%)	1.000
Liver herniation	8/26 (30.8%)	7/26 (26.9%)	0.760
Severe CVM	12 (46.2%)	26 (86.7%)	0.001

BW, birthweight; CDH, congenital diaphragmatic hernia; CVM, cardiovascular malformations; GA, gestational age.

In various studies, the prevalence of CVM ranges from 8 to 13 per 1000 live births.[13,14] However, a recent study suggested a much higher prevalence of CVM (50 per 1000 live births).[15] The

Table 3 Clinical characteristics of infants according to status at discharge. Data are presented as mean values ± SD or median values and (Q1–Q3)

Variables	Survival without morbidity	Survival with morbidity or death	*P*
Number of infants	13	43	
GA (wk)	37.4 ± 1.6	37.2 ± 2.7	0.787
BW(g)	2158 ± 535	2421 ± 584	0.154
Apgar score at 1 min	4 (3–6.3)	3 (2–4)	0.047
Apgar score at 5 min	5 (5–7)	5 (2.3–6)	0.068
Female	8 (61.5%)	22 (51.1%)	0.511
Vaginal delivery	1 (7.7%)	9 (20.9%)	0.424
Prenatal diagnosis	11 (84.6%)	34 (79.1%)	0.721
CDH left	12 (92.3%)	39 (90.7%)	1.000
Liver herniation	3/13 (23.1%)	12/39 (30.8%)	0.733
Severe CVM	4 (30.8%)	34 (79.1%)	0.001

BW, birthweight; CDH, congenital diaphragmatic hernia; CVM, cardiovascular malformations; GA, gestational age.

Table 4 Association of severity of CVM and CDH with status at discharge (multivariable logistic regression). Variables were adjusted for gestational age, prenatal diagnosis, and Apgar score at 1 min

Variables	Mortality		Morbidity	
	Adjusted OR	95%CI	Adjusted OR	95%CI
Severe CVM	7.69	2.00–30.27	7.93	1.76–35.79
Liver herniation	0.49	0.12–1.91	0.82	0.15–4.63

CVM, cardiovascular malformation.

Table 5 Survival rates with and without morbidity at discharge for infants with CDH according to presence and type of cardiac defect

		n	Survivors	Survivors without morbidity
CDH with CVM	Overall	56	26 (46.4%)	13 (23.2%)
	Severe	38	12 (31.6%)	4 (10.5%)
	Mild	18	14 (77.8%)	9 (50.0%)
VSD		18	13 (72.2%)	7 (38.9%)
TOF or DORV with RVOTO		9	3 (33.3%)	1 (11.1%)
DORV without RVOTO		5	2 (40.0%)	1 (20%)
CoA or IAA		7	3 (42.9%)	2 (28.6%)
HLHS		6	0	0
SV		4	2 (50%)	0
PS or PA		2	1 (50%)	1 (50%)
AVSD		1	0	0
TAPVR		1	0	0
TGA		1	1 (100%)	0
TA		1	1 (100%)	1 (100%)
TV dysplasia		1	0	0

AVSD, atrioventricular septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; CVM, cardiovascular malformation; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interruption of the aortic arch; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricular tract obstruction; SV, single ventricle; TA, tricuspid valve atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

present study detected a frequency of CVM associated with CDH of about twice as high as that in the general population. The frequency of this study (12%) was similar to that identified by the Congenital Diaphragmatic Hernia Study Group (CDHSG) (10.5%).[5] In the assessment of types of CVM, VSD was the most common in both studies (this study 32%, CDHSG study 42%). The frequency of left-sided heart disease, including HLHS, was 28% in the CDHSG study, which was higher than that identified in the present study (19.7%). Some reports have shown a lower frequency of left-sided heart disease in Asia than in Western countries. Thus, the discrepancy between our results and those of the CDHSG study may be because of differences in race.[15,16] In Japan, left-sided heart disease accounts for about 3% of all CVM, which suggests that the frequency of left-sided heart disease associated with CDH is extremely high, even in the Japanese population.[15,17]

In a study of major structural non-cardiac anomalies identified with CVM, Miller *et al.* reported a frequency of 15% for left-sided heart disease associated with all congenital anomalies. In another study, the frequency of left-sided heart disease associated with CDH was reported as 27%.[18] The higher incidence of left-sided heart disease may reflect the limited flow through the left side of the heart due to direct compression of herniated structures and decreased pulmonary blood flow caused by lung compression. In the present study, all infants with left-sided heart disease also had left-sided CDH, which supports this theory.[19,20]

In this study, numerous conotruncal anomalies, such as TOF and DORV, were observed, accounting for about 30% of all CVM. Trisomy 13 and trisomy 18 have been strongly associated with conotruncal anomalies.[21] Our sample included 14 infants with trisomy 13 and trisomy 18, half of whom had TOF or DORV. This may be one of the causes of the high frequency of conotruncal anomalies.

Many studies have reported associations between the prognosis for patients with isolated CDH and several predictors, such as lung-to-head ratio, liver herniation, low birthweight, Apgar score, pulmonary artery diameter, and best PaO_2 value.[8–12,22] This study found no association between liver herniation (used to represent severe CDH) and mortality and morbidity. However, the results indicated that severity of CVM was an independent risk factor for mortality and morbidity at discharge.

In this study, the survival rate of infants with mild CVM was about 80%, the same as that for isolated CDH (84%) in our survey.[23] On the other hand, the survival rate of infants with severe CVM was about 30% and of infants without morbidity was just 10%. This result suggests that the prognosis remains poor in infants with CDH concurrent with CVM despite improvements in outcomes in cases with isolated CDH. Furthermore, in our survey, the usage rates of ECMO and iNO in all CDH were 7.0% and 56.2%, respectively.[23] The usage rates among infants with both CDH and CVM tended to be higher than those among all CDH.

The survival rate was relatively favorable in infants with VSD (72%) but not in infants with other types of CVM (<50%). In infants with VSD, cyanosis rarely develops. However, in infants with univentricular anatomy, DORV, and pulmonary stenosis, cyanosis could develop easily even without CDH. Furthermore, in such patients, hypoxia could get worse because of presence of CDH. It may be one of the causes that infants with CDH and such types of CVM have poorer prognosis than those with VSD.

In this study, none of the six infants with HLHS survived. Termination of labor and palliative care after birth may be considered in cases associated with HLHS. Although the survival rate of infants with VSD was favorable, only 40% of infants were discharged from hospital without morbidities. This may be important information for parents of infants with this defect.

Completion of Fontan circulation is difficult for infants with CVM in whom biventricular repair is also difficult. Residual pulmonary hypertension complicates this situation. Therefore, 3- or 5-year survival rates may be lower than the survival rate at discharge used in this study. To our knowledge, no previous cases have been reported of survival in infants with cavopulmonary anastomosis and CDH. Long-term follow up in patients with these conditions is required.

This study has several limitations. First, detailed information regarding treatment was not included. This study was based on data from a retrospective national survey of infants with CDH that did not include this information. Second, severity of CVM was defined on the basis of hemodynamic significance. However, this decision may have differed between facilities, and thus, assessment of disease severity may not have been uniform. Third, the end-point of the study was at discharge; therefore, intracardiac surgery had not yet been performed in some infants. Thus, the actual mortality and morbidity rates may have been poorer than those reported in this study. Finally, the number of cases

may be insufficient for accurate evaluation of prognostic factors. The lung-to-heart ratio and pulmonary artery size are useful for assessing severity of CDH; however, data on these parameters were available for only about 20 infants included in this study. Thus, liver herniation was used as an index of CDH severity.

Despite these limitations, the results of this study demonstrate that the frequency of CVM among infants with CDH in Japan is similar to that in Western countries. Mortality and morbidity rates remain unfavorable despite improvements in perinatal management. The severity of CVM is important to the prognosis for patients who have these conditions concurrently. Further study is needed to determine factors influencing prognosis depending on the type of CVM.

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References

1 Tracy ET, Mears SE, Smith PB *et al.* Protocolized approach to the management of congenital diaphragmatic hernia: benefits of reducing variability in care. *J. Pediatr. Surg.* 2010; **45**: 1343–8.
2 Su W, Berry M, Puligandla PS, Aspirot A, Flageole H, Laberge JM. Predictors of gastroesophageal reflux in neonates with congenital diaphragmatic hernia. *J. Pediatr. Surg.* 2007; **42**: 1639–43.
3 Kitano Y, Okuyama H, Saito M *et al.* Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: a multicenter survey in Japan. *Ultrasound Obstet. Gynecol.* 2011; **37**: 277–82.
4 Zaiss I, Kehl S, Link K *et al.* Associated malformations in congenital diaphragmatic hernia. *Am. J. Perinatol.* 2011; **28**: 211–18.
5 Graziano JN. Cardiac anomalies in patients with congenital diaphragmatic hernia and their prognosis: a report from the Congenital Diaphragmatic Hernia Study Group. *J. Pediatr. Surg.* 2005; **40**: 1045–9; discussion 1049.
6 Fauza DO, Wilson JM. Congenital diaphragmatic hernia and associated anomalies: their incidence, identification, and impact on prognosis. *J. Pediatr. Surg.* 1994; **29**: 1113–17.
7 Cohen MS, Rychik J, Bush DM *et al.* Influence of congenital heart disease on survival in children with congenital diaphragmatic hernia. *J. Pediatr.* 2002; **141**: 25–30.
8 Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictors of survival in fetal diaphragmatic hernia. *J. Pediatr. Surg.* 1996; **31**: 148–51; discussion 151.
9 Mullassery D, Ba'ath ME, Jesudason EC, Losty PD. Value of liver herniation in prediction of outcome in fetal congenital diaphragmatic hernia: a systematic review and meta-analysis. *Ultrasound Obstet. Gynecol.* 2010; **35**: 609–14.
10 Lipshutz GS, Albanese CT, Feldstein VA *et al.* Prospective analysis of lung-to-head ratio predicts survival for patients with prenatally diagnosed congenital diaphragmatic hernia. *J. Pediatr. Surg.* 1997; **32**: 1634–6.
11 Estimating disease severity of congenital diaphragmatic hernia in the first 5 minutes of life. The Congenital Diaphragmatic Hernia Study Group. *J. Pediatr. Surg.* 2001; **36**: 141–5.
12 Suda K, Bigras JL, Bohn D, Hornberger LK, McCrindle BW. Echocardiographic predictors of outcome in newborns with congenital diaphragmatic hernia. *Pediatrics* 2000; **105**: 1106–9.

13 Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. *Circulation* 1971; **43**: 323–32.
14 Meberg A, Otterstad JE, Frøland G, Lindberg H, Sørland SJ. Outcome of congenital heart defects–a population-based study. *Acta Paediatr.* 2000; **89**: 1344–51.
15 Ishikawa T, Iwashima S, Ohishi A, Nakagawa Y, Ohzeki T. Prevalence of congenital heart disease assessed by echocardiography in 2067 consecutive newborns. *Acta Paediatr.* 2011; **100**: e55–60.
16 Wu MH, Chen HC, Lu CW, Wang JK, Huang SC, Huang SK. Prevalence of congenital heart disease at live birth in Taiwan. *J. Pediatr.* 2010; **156**: 782–5.
17 Nakazawa M, Seguchi M, Takao A. Prevalence of congenital heart disease in Japanese children. *J Jpn Pediatr Soc* 1986; **90**: 2578–86.
18 Miller A, Riehle-Colarusso T, Alverson CJ, Frías JL, Correa A. Congenital heart defects and major structural noncardiac anomalies, Atlanta, Georgia, 1968 to 2005. *J. Pediatr.* 2011; **159**: 70–8.
19 Vogel M, McElhinney DB, Marcus E, Morash D, Jennings RW, Tworetzky W. Significance and outcome of left heart hypoplasia in fetal congenital diaphragmatic hernia. *Ultrasound Obstet. Gynecol.* 2010; **35**: 310–17.
20 Baumgart S, Paul JJ, Huhta JC *et al.* Cardiac malposition, redistribution of fetal cardiac output, and left heart hypoplasia reduce survival in neonates with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation. *J. Pediatr.* 1998; **133**: 57–62.
21 Maeda J, Yamagishi H, Furutani Y *et al.* The impact of cardiac surgery in patients with trisomy 18 and trisomy 13 in Japan. *Am. J. Med. Genet. A* 2011; **155A**: 2641–6.
22 Germain JF, Farnoux C, Pinquier D *et al.* Can blood gas values predict pulmonary hypoplasia in antenatally diagnosed congenital diaphragmatic hernia? *J. Pediatr. Surg.* 1996; **31**: 1634–9.
23 Nagata K, Usui N, Kanamori Y *et al.* The current profile and outcome of congenital diaphragmatic hernia: a nationwide survey in Japan. *J. Pediatr. Surg.* 2013; **48**: 738–44.

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The current profile and outcome of congenital diaphragmatic hernia: A nationwide survey in Japan ☆

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Abstract

Background/Purpose: Few nationwide surveys have been reported regarding the perinatal status, clinical course and postnatal outcome of cases with congenital diaphragmatic hernia (CDH). The aim of this study was to review the current profile and the outcomes of a large cohort of CDH cases in Japan.

Methods: A nationwide retrospective cohort study was conducted on neonates diagnosed to have CDH between January 2006 and December 2010. The questionnaires were sent to 159 representative regional institutions and 109 (68.6%) institutions responded to the preliminary survey which had 674 cases. Eleven institutions which had 60 CDH neonates did not respond to the second questionnaire, and 26 institutions had no cases. Finally, 614 CDH neonates from 72 institutions had been collected and were used in the detailed survey. The perinatal status, clinical course and the postnatal outcome were reviewed. Survival was defined as infants alive at hospital discharge, at the time of transfer or still in the hospital at the time of questionnaire, which was confirmed during the period from July 2011 to November 2011 by the investigators.

Results: Four hundred sixty-three (75.4%) of 614 CDH neonates survived in this study. The overall survival rate of neonates with isolated CDH was 84.0%. A total of 444 (72.0%) patients were prenatally diagnosed, and had a survival rate of 70.8%. Four hundred thirty-three (70.9%) patients were treated with high-frequency oscillatory ventilation (HFOV) as the initial ventilation, 344 (56.0%) patients

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received inhaled nitric oxide (iNO) and 43 (7.0%) required extracorporeal membrane oxygenation (ECMO). The overall survival rates of the CDH neonates who had been treated using HFOV, iNO and ECMO were 74.3%, 68.3% and 37.2%, respectively.

Conclusions: This study demonstrated that the current status for CDH treatment in Japan and the overall survival rate were comparable to those of recent reports from other countries.

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm, which occurs in between 1 in 2500 to 4000 live births [1–3]. The main causes of mortality from CDH are pulmonary hypoplasia and pulmonary hypertension [4]. During the past decades, there have been advances in the technologies used for neonatal intensive care, such as the development of exogenous surfactant, inhaled nitric oxide (iNO), high-frequently oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO). Also, with the advent of the "gentle ventilation," there have been several reports from single institutions that indicated improvements in the outcome for CDH patients, with survival rates up to 80% to 90% [5–7]. However, the Congenital Diaphragmatic Study Group, and their largest multi-center and multi-country based studies showed a survival rate of roughly 70% for infants with CDH [8,9]. Several population-based studies have also advocated that there has been "hidden mortality" of the CDH patients, and that the data analysis should be treated cautiously [10,11].

The relative rarity of CDH makes conducting well-designed clinical studies extremely difficult, because no single institution can accrue sufficient patients to reach meaningful conclusions. Therefore, the management strategy for CDH has evolved based on retrospective studies from multiple centers using different treatment strategies, as typified by the Congenital Diaphragmatic Hernia Study Group [8,9,12–17].

In Japan, there was multi-center retrospective cohort study for antenatally diagnosed CDH which was reported in several papers [18–21]. Therefore, clinicians had recognized the need for a large cohort study to better understand this complicated disease. The purposes of this study were to document the current profiles and outcomes of CDH neonates and to analyze the treatment strategies that were performed for Japanese CDH neonates over the past 5 years in Japan.

1. Materials and methods

This retrospective survey was approved by the ethics committees of the six representative institutions, including the Graduate School of Medical Sciences, Kyushu University, Osaka University Graduate School of Medicine, National Center for Child Health and Development, Nagoya University Hospital, Hyogo College of Medicine and Osaka Medical Center and Research Institute for Maternal and Child Health (representative institutional review board approval no. 23-52, Kyushu University Graduate School of Medical Sciences).

This nationwide cohort study was designed to use the retrospectively collected data of CDH neonates who were born between January 2006 and December 2010. Questionnaires were sent to 159 hospitals, which were associated with the authorized institutions of the Japanese Society of Pediatric Surgeons, or were perinatal medical centers for neonates from all over Japan. A total of 109 centers (68.6%) responded to the preliminary survey, and there were 674 CDH neonates diagnosed during the 5-year period. Eleven institutions that had 60 CDH neonates did not respond to the second questionnaire, and 26 institutions had no cases. Finally, 72 institutions (45.3%) that had 614 CDH neonates consented to participate in our survey.

The CDH infants whose diagnosis was over 28 days after birth were excluded in this study. Because of the questionnaire nature of the survey, the patient data were not complete for all variables. Survival was defined as infants who were alive at hospital discharge, transferred to another facility or still alive at the hospital, which was confirmed during the period from July 2011 to November 2011 by the investigators. The other outcomes such as the need for home oxygen therapy (HOT), home mechanical ventilation (HMV), home parental nutrition (HPN) and home enteral nutrition (HEN) were also recorded.

The patient demographics, including the year of birth, the outcome, the presence of a prenatal diagnosis, sex, birth location, mode of delivery, gestational age at delivery and birth weight were reviewed. The side of the defect, the presence of other anomalies, including major or minor cardiac anomalies and severe chromosomal anomalies, were also reviewed. An isolated CDH was defined as a CDH without any associated life-threatening or severe chromosomal anomalies [18]. A major cardiac anomaly was defined as a life-threatening cardiac anomaly that has a profound impact on the circulatory dynamics. A minor cardiac anomaly was defined as a cardiac anomaly that did not affect the outcome. A severe chromosomal abnormality was defined as a lethal chromosomal abnormality.

According to the prenatal variables, the lung-to-head ratio (LHR) was measured by multiplication of the longest diameter of the lung by its longest perpendicular diameter in the cross-sectional plane at the level of the four-chamber

view of the heart [18]. The lung-to-thorax transverse ratio (L/T ratio) was defined as the area of the contralateral lung, which was determined by tracing around the contralateral lung, divided by the area of the thorax surrounded by the inner border of the bilateral ribs, the sternum and the vertebra [21]. Polyhydramnios was defined as a maximum depth of amniotic fluid over 8 cm. Fetal hydrops was defined as the presence of ascites, pleural effusion, or skin edema during fetal ultrasonography. The risk classification of Kitano et al. [18] was the prenatal risk classification which was used to estimate the intact discharge rate according to the fetal stomach position and liver position. The risk classification of Usui et al. [21] was the prenatal risk classification which was used to estimate the 90-day-survival using the L/T ratio and the fetal liver position.

The postnatal variables were the therapeutic variables and the surgical findings. The defect size was determined with reference to the schema provided by CDH Study Group, as previously reported in the literature [9]. The subsequent analyses were performed to analyze the correlations between the survival rates and the prenatal or postnatal variables.

The frequencies and percentages were used to describe the categorical data. The χ^2 test and Fisher's exact test were used for the analysis of the categorical data. The data were also expressed as the medians (range). A P value of <0.05 was considered to indicate a statistically significant difference. The statistical analyses were performed using the JMP software program (version 9; SAS Institute, Inc, Cary, NC).

2. Results

The annual numbers and the survival rates of CDH neonates during this 5-year period are shown in Fig. 1. There were no statistically significant differences among the survival rates in terms of chronology.

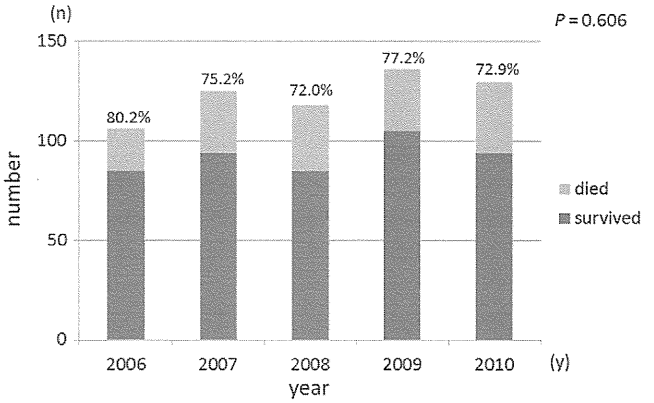

Fig. 1 The number of patients for each year appears at the top of each bar, and the survival rate is noted in brackets. The light color indicates the numbers of patients who died, and the dark color indicates the surviving patients. There were no significant differences in the survival rates according to year. ($P<0.606$).

Table 1 The demographics and survival rates of the CDH patients.

Variables	Distribution of patients (%)	Survival rate (%) and P value
All patients ($n=614$)	614 (100)	463 (75.4)
Prenatal diagnosis ($n=614$)		$P<0.001$
Yes	442 (72.0)	313 (70.8)
No	172 (28.0)	150 (87.2)
Sex ($n=614$)		$P=0.64$
Female	283 (46.0)	216 (76.3)
Male	331 (54.0)	247 (74.6)
Birth location ($n=614$)		$P<0.001$
Inborn	449 (73.1)	320 (71.3)
Outborn	165 (26.9)	143 (86.7)
Mode of delivery ($n=614$)		$P=0.043$
Vaginal	235 (38.3)	188 (80.0)
C-section	379 (61.7)	275 (72.6)
Gestational age ($n=614$)		$P<0.001$
<37 weeks	124 (20.2)	74 (59.7)
≥37 weeks	490 (79.8)	389 (79.4)
Birth weight ($n=613$)		$P<0.001$
<2 kg	68 (11.1)	33 (48.5)
≥2 kg	545 (88.8)	430 (78.9)
Isolated CDH ($n=614$)		$P<0.001$
Yes	520 (84.7)	437 (84.0)
No	94 (15.3)	26 (27.7)
Side of hernia ($n=614$)		$P<0.001$
Left	553 (90.1)	425 (76.9)
Right	57 (9.3)	38 (66.7)
Bilateral	4 (0.6)	0 (0)
Cardiac anomaly ($n=614$)		$P<0.001$
Major	56 (9.1)	12 (21.4)
Minor	52 (8.5)	43 (82.7)
None	506 (84.7)	408 (80.6)
Severe chromosomal anomaly ($n=614$)		$P<0.001$
Yes	39 (6.4)	8 (20.5)
No	575 (93.6)	455 (79.1)

The demographic data of this study are shown in Table 1. The overall survival rate was 75.4%. The prenatal diagnosis, birth location, gestational age, birth weight, isolated CDH, side of hernia, the presence of major cardiac anomalies and the presence of severe chromosomal abnormalities were likely to affect the outcome.

Other information associated with these demographic data was as follows. The median gestational age at delivery was 265 days (range, 161–293 days). The median birth weight was 2740 g (range, 538–5246 g). A total of 9.1% of the neonates with CDH had a major cardiac anomaly; 8.5% had a minor cardiac anomaly. Of the 56 major cardiac anomalies, 13 involved a double-outlet right ventricle, 10 had a ventricular septal defect, 7 had hypoplastic left heart syndrome, tetralogy of Fallot was present in 6, there was a single ventricle in 5, coarctation of the aorta was present in 5, pulmonary atresia was present in 2, endocardial cushion

defect was present in 2, tricuspid atresia was present in 2, transposition of the great arteries was present in 1, an interrupted aortic arch was present in 1, total anomalous pulmonary venous return was present in 1, and the pulmonary trunk was affected in 1. With regard to the severe chromosomal abnormalities, 6.4% of the neonates had a severe chromosomal anomaly. Of these 36 patients with a severe chromosomal abnormality, trisomy 18 syndrome was noted in 15, trisomy 13 syndrome in 7, trisomy 3 syndrome in 3, tetrasomy 12p in 3, a deletion of 10p, 9p, and 4p in 1, trisomy 9 syndrome in 1, XXX syndrome in 1, a sex chromosomal abnormality in 1, and 45 X syndrome in 1.

Four hundred forty-four CDH neonates (72.6%) survived to discharge, although three neonates died after discharge. One hundred forty-eight CDH neonates (24.1%) died in the hospital. Eighteen CDH neonates had been transferred, and two CDH neonates were still in the hospital. The other outcomes at discharge were as follows: 41 CDH neonates (8.8%) needed HOT, 8 (1.7%) needed HMV, 39 (8.4%) needed HEN and 2 (0.4%) needed HPN.

The relationships between the prenatal prognostic variables and the survival rates are shown in Table 2. The numbers do not always add up to 614 due to some missing values.

According to the prenatal diagnostic valuables, polyhydramnios and some signs of hydrops were likely to affect the outcome. Liver herniation was one of the most reliable prognostic factors for the prenatal diagnosis, and 26.9% of the CDH neonates were recognized to have this sign in the present study. An LHR<1.0 and an L/T ratio<0.08 were also the most reliable prognostic factors in the prenatal diagnosis.

Table 2 The correlations between the survival rate and the prenatal diagnostic variables.

Variables	Distribution of patients (%)	Survival rate (%) and *P* value
Polyhydramnios (n=400)		P<0.001
Yes	125 (31.3)	67 (53.6)
No	275 (68.7)	217 (78.9)
Hydrops (n=409)		P<0.001
Yes	22 (5.3)	7 (31.8)
No	393 (94.7)	290 (73.8)
Liver herniation (n=409)		P<0.001
Yes	110 (26.9)	60 (54.6)
No	299 (73.1)	234 (78.3)
LHR (n=240)		P<0.001
<1.0	24 (10.0)	7 (29.2)
≥1.0	216 (90.0)	177 (81.9)
L/T ration (n=231)		P<0.001
<0.08	71 (30.7)	36 (50.7)
≥0.08	160 (69.3)	141 (88.1)
Kitano's sick classification (n=394)		P<0.001
Group I	285 (72.3)	225 (79.0)
Group II	70 (17.8)	43 (61.4)
Group III	39 (9.9)	17 (43.6)
Usui's sick classification (n=228)		P<0.001
Group A	129 (56.6)	225 (79.0)
Group B	58 (25.4)	36 (62.1)
Group C	41 (18.0)	19 (46.3)

Table 3 The correlations between the survival rates and the postnatal treatment variables.

Variables	Distribution of patients (%)	Survival rate (%) and *P* value
Initial mode of ventilation (n=545)		P<0.001
HFOV	435 (79.8)	323 (74.3)
CMV	110 (20.2)	100 (90.9)
NO inhalation (n=612)		P<0.001
Yes	344 (56.2)	235 (68.3)
No	268 (43.8)	227 (84.7)
ECMO (n=614)		P<0.001
Yes	43 (7.0)	16 (37.2)
No	571 (93.0)	447 (78.3)
Operation (n=614)		P<0.001
Yes	530 (86.3)	463 (87.4)
No	84 (13.7)	0 (0)
Approach (n=526)		P=0.806
Abdominal	516 (97.4)	463 (87.4)
Thoracic	10 (1.9)	9 (90.0)
Hernia sac (n=515)		P=0.853
Yes	77 (14.8)	66 (85.7)
No	438 (85.2)	382 (87.2)
Diaphragmatic closure (n=522)		P<0.001
Direct repair	384 (62.5)	361 (94.0)
Patch repair	138 (22.5)	97 (70.3)
Defect size (n=524)		P<0.001
A	93 (15.1)	90 (96.8)
B	282 (45.9)	263 (93.3)
C	117 (19.1)	88 (75.2)
D	32 (5.2)	16 (50)

With regard to the prenatal risk stratification, the classifications of Kitano et al. and Usui et al. were the most reliable risk stratification systems for these Japanese cases. In both of these risk stratification systems, there were significant differences in the survival rates with increases in the severity.

The relationships between the postnatal treatment variables and the survival rates are shown in Table 3. With regard to the initial ventilation mode, HFOV and the conventional mode of ventilation were applied in 70.9% (n=435/545, 1 had spontaneous breathing and was excluded) and 17.9% (n=110/545) of cases, respectively. A total of 56.2% of the CDH neonates were administered iNO. Only 7.0% of the CDH neonates were treated with ECMO.

With regard to the operation, 86.3% of the CDH neonates underwent an operation. The survival rate of the surgically treated CDH neonates was 87.4%. Among the CDH neonates

who underwent surgery, 98.1% (n=516/526, 4 CDH neonates were excluded: 1 was treated laparoscopically and 3 were treated by thoracoscopically) were treated via a transabdominal approach and 1.9% were treated via a transthoracic approach. The timing of the operation and the survival rate at each age are listed in Fig. 2. The survival rates decreased over time after 96 h had elapsed from birth. The median age at the time of the operation was 61 h (range; 30–99), and the average age at the time of the operation was 98 h.

With regard to the presence of the hernia sac in the surgical findings, 14.8% of the CDH neonates had the hernia sac present and 85.2% had no sac. A total of 62.5% of the CDH neonates (n=384/522, missing data=1, 7 excluded: 4 were treated using a muscle flap procedure, 3 were treated in other ways) were closed directly with their own diaphragm. The defect size in this study also exhibited a strong correlation with the survival rates, and this finding correlated with those previously reported in the literature [8].

3. Discussion

This study was the first Japanese nationwide multi-center survey to collect and analyze a large numbers of CDH neonates who were born between 2006 and 2010. In these 614 CDH neonates, the patient demographics, correlations between survival rates and prenatal or postnatal variables were retrospectively reviewed. The aims of this study were two-fold. First, this study was designed to provide useful information for parents and clinicians when the CDH neonates are diagnosed prenatally. Second, this study was designed to provide evidence for the feasibility of determining a standardized treatment protocol and for carrying out evidence-based prospective studies.

In our series, 70.2% of the CDH neonates were prenatally diagnosed, 73.1% were born in the hospital and the 61.7% were delivered by cesarean section. The CDH Study Group

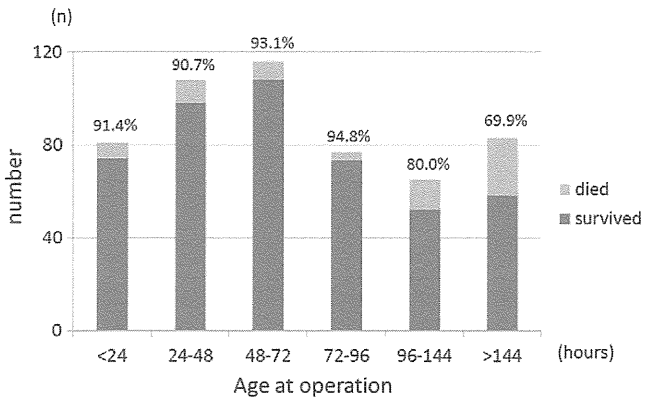

Fig. 2 The number of patients according to the timing of the operation is indicated on the top of each bar, and the survival rate is noted in brackets. The light color indicates the number of patients who died, and the dark color indicates the surviving patients.

reported that 51.7% of CDH neonates were prenatally diagnosed, and the rate of birth at their own center was 38.5% [8]. Stevens et al. [15] also reported that the rates of inborn and cesarean section delivery for the prenatally diagnosed CDH cases were 60.5% and 48.3%, respectively. Therefore, Japanese CDH neonates may have a tendency to be prenatally diagnosed, and were often delivered in tertiary centers and born by cesarean section. However, the apparent impact of prenatal detection may be biased by "hidden mortality," including termination of pregnancy, intrauterine fetal death and death occurring before admission to the tertiary centers [2,3,10,11].

The prenatal detection of polyhydramnios, hydrops, liver herniation, an LHR<1.0 and an L/T ratio<0.08 were considered prognostic risk factors. the risk classifications of Kitano et al. and Usui et al. were considered to be useful, because the survival rates correlated closely with each level of risk stratification by these systems. However, the most profound problem with the prenatal diagnosis in this study was that one-third of the positional relationships and more than half of the LHR and L/T ratios were not reported; nevertheless, 70.2% of the CDH neonates were prenatally diagnosed. This discrepancy might be caused by the absence of the prenatal diagnostic system in Japan which is still not obligated during the prenatal period. In Japan, there may be some limitations in the accuracy of the lung measurements by ultrasonography because CDH fetuses are not fully centralized to the perinatal centers and experienced investigators are not always present in the regional institutions. The classification of Kitano et al. [18] is an easier-to-use prenatal classification and is likely to become used more often because physicians are required to detect only the liver and stomach position. It is necessary to establish a risk stratification system and then to validate the standardized protocol including fetal therapy in the near future.

HFO, iNO and ECMO were performed in 435 (70.9%), 344 (56.2%) and 43 (7.0%) patients, respectively. The characteristics of the Japanese trend in CDH treatment were that HFOV and iNO were frequently used, and that ECMO was not frequently used. Miglizza et al. [22] described their protocol, which begins with elective HFOV, and they also reported an improved survival rate and a lower incidence of chronic lung disease. The indications for iNO were not strictly defined, but it was used without hesitation in almost all institutions in Japan. When the CDH neonates have a slight difference between their pre-ductal and post-ductal oxygen saturation, iNO is immediately administered to reduce the pulmonary artery resistance and subsequently reduce the right ventricle's afterload [6,21]. The CDH Study Group also demonstrated that there was a trend toward a significantly increased use of iNO and a decreased use of ECMO in recent years [13]. Of note, a discrepancy was present because the survival rates did not increase, despite the introduction of these advanced therapies. Therefore, large prospective studies, such as the VICI trial within the CDH EURO Consortium, may be necessary to provide further

Table 4 The overall and isolated survival rates of the CDH patients reported in previous studies.

Author and year of publication	Country	Study period	Study design	Overall survival rate (%)	Isolated survival rate (%)
Boloker et al., 2002 [5]	USA	1992–2000	Retrospective, single institution	91/120 (75.8)	NA
Javid et al., 2004 [7]	Canada	1996–1997	Prospective, multi-center	73/88 (83.0)	NA
Gallot et al., 2007 [3]	French	1986–2003	Population based, multi-center	235/387 (60.7)	199/285 (69.8)
The CDH Study Group, 2007 [8]	USA, etc.	1995–2004	Retrospective, multi-center	2100/3062 (68.6)	NA
Migliazza et al., 2007 [22]	Italy	1994–2005	Retrospective, single institution	77/111 (69.4)	NA
Lazar et al., 2011 [25]	USA	2004–2009	Retrospective, single institution	NA	85/116 (73.3)
Present study, 2012	Japan	2006–2010	Retrospective, nationwide	463/614 (75.4)	437/520 (84.0)

Abbreviation: NA=not available.

evidence-based insights into the optimal ventilation strategies for CDH patients [23,24].

With regard to the operation, the trans-abdominal approach was the standard procedure for CDH, and the presence of a hernia sac was not a predictive factor for the outcome. Patch repair and the defect size both affected the outcome, as previously reported in the literature [8,9,13]. While the defect size is a favorable marker for the degree of pulmonary hypoplasia, it may also correlate with the severity of pulmonary hypertension [8,9,13]. Controversy remains regarding the timing of the surgical repair in CDH patients. In the majority of successful centers, surgeons delayed repair until physiological stabilization and improvement in pulmonary hypertension [4–6,22–25]. However, because the severity of CDH patients and the criteria regarding the timing of the operation differed in this study, therefore, risk stratification, the protocol-based treatment strategy and prospective study will thus be needed to draw a more credible conclusion.

The prognosis of large cohorts of CDH patients which was recently published in the literature is shown in Table 4 [3,5,7,8,22,25]. These data should be carefully interpreted, because the rates of termination and in utero death differed in the different regions, and the treatment strategies often varied in the individual institutions [13]. Nevertheless, the overall and isolated survival rates in the present study were 75% and 84%, respectively, which compared favorably with the rates of previous studies from other countries.

A major limitation of this study is the retrospective study design. Many centers had a small number of cases and the variables were analyzed only by a descriptive study. The CDH EURO Consortium documented their standardized protocol with their final consensus, and checked the individual levels of evidence and grades of recommendation according to the SIGN criteria [23]. Almost all treatment recommendations resulted in a grade level of D, which implies that the CDH treatments were lacking in evidence and were therefore based on the individual institutional experiences. The overall survival rates of this study were comparable to the previous reports; however, establishing a standardized protocol based on a prenatal risk stratification system may be necessary to define and validate such a comprehensive treatment strategy.

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(Kagoshima); Kakogawa West City Hospital (Kakogawa); Kanazawa Medical University Hospital (Kahoku); Kansai Medical University Hirakata Hospital (Hirakata); Kawasaki Medical School Hospital (Kurashiki); Keio University Hospital (Tokyo); Kimitsu Chuo Hospital (Kisarazu); Kinki University Hospital (Osakasayama); Kitakyushu Municipal Medical Center (Kitakyushu); Kitasato University Hospital (Sagamihara); Kobe University Hospital (Kobe); Kumamoto City Hospital (Kumamoto); Kumamoto University Hospital (Kumamoto); Kurume University Hospital (Kurume); Kyorin University Hospital (Mitaka); Kyoto University Hospital (Kyoto); Kyushu University Hospital (Fukuoka); Matsudo City Hospital (Matsudo); Mie University Hospital (Tsu); Miyagi Children's Hospital (Sendai); Nagano Children's Hospital (Nagano); Nagasaki University Hospital (Nagasaki); Nagoya University Hospital (Nagoya); Nara Hospital Kinki University Faculty of Medicine (Ikoma); Nara Medical University Hospital (Kashihara); National Center for Child Health and Development (Tokyo); Niigata City General Hospital (Niigata); Niigata Prefectural Central Hospital (Niigata); Niigata University Medical and Dental Hospital (Niigata); Nikko Memorial Hospital (Muroran); Ogaki Municipal Hospital (Ogaki); Ohta General Hospital (Koriyama); Oita Prefectural Hospital (Oita); Omihachiman Community Medical Center (Omihachiman); Osaka City General Hospital (Osaka); Osaka Medical Center and Research Institute for Maternal and Child Health (Izumi); Osaka University Hospital (Suita); Saga Prefectural Hospital Koseikan (Saga); Saitama Medical Center (Kawagoe); Saitama Medical University Hospital (Iruma); Shimane Prefectural Central Hospital (Izumo); Showa University Hospital (Tokyo); St. Marianna University School of Medicine Hospital (Kawasaki); Takatsuki General Hospital (Takatsuki); Tokai University Hospital (Isehara); Tokushima University Hospital (Tokushima); Tokyo Metropolitan Children's Center (Fuchu); Tokyo Women's Medical University Yachiyo Medical Center (Yachiyo); Tottori University Hospital (Yonago); Tsuchiura Kyodo General Hospital (Tsuchiura); Tsukuba University Hospital (Tsukuba); and University of Miyazaki Hospital (Miyazaki).

References

[1] Colvin J, Bower C, Dickinson JE, et al. Outcomes of congenital diaphragmatic hernia: a population-based study in Western Australia. Pediatrics 2005;116:356-63.

[2] Yang W, Carmichael SL, Harris JA, et al. Epidemiologic characteristics of congenital diaphragmatic hernia among 2.5 million California. Birth Defects Res A Clin Mol Teratol 2006;76:170-4.

[3] Gallot D, Boda C, Ughettto S, et al. Prenatal detection and outcome of congenital diaphragmatic hernia: French registry-based study. Ultrasound Obstet Gynecol 2007;29:276-83.

[4] Logan JW, Rice HE, Goldberg RN, et al. Congenital diaphragmatic hernia: a systemic review and summary of best-evidence practice strategies. J Perinatol 2007;27:535.

[5] Boloker J, Bateman DA, Wung JT, et al. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. J Pediatr Surg 2002;37:357-66.

[6] Masumoto K, Teshiba R, Esumi G, et al. Improvement in the outcome of patients with antenatally diagnosed congenital diaphragmatic hernia using gentle ventilation and circulatory stabilization. Pediatr Surg Int 2009;25:487-92.

[7] Javid PJ, Jaksic T, Skarsgard ED, et al. Survival rate in congenital diaphragmatic hernia: the experience of the Canadian Neonatal Network. J Pediatr Surg 2004;39:657-60.

[8] The Congenital Diaphragmatic Hernia Study Group. Defect size determines survival in infants with congenital diaphragmatic hernia. Pediatrics 2007;120:e651-7.

[9] Tsao K, Lally KP. The congenital diaphragmatic hernia study group: a voluntary international registry. Semin Pediatr Surg 2008;17:90-7.

[10] Stege G, Fenton A, Jaffray B. Nihilism in the 1990's: the true mortality of congenital diaphragmatic hernia. Pediatrics 2003;112:532-5.

[11] Mah VK, Chiu P, Kim P. Are we making a real difference? Update on 'Hidden mortality' in the management of congenital diaphragmatic hernia. Fetal Diagn Ther 2011;29:40-5.

[12] The Congenital Diaphragmatic Study Group. Surfactant does not improve survival rate in preterm infants with congenital diaphragmatic hernia. J Pediatr Surg 2004;39:829-33.

[13] The Congenital Diaphragmatic Hernia Study Group. Treatment evolution in high-risk congenital diaphragmatic hernia. Ten years' experience with diaphragmatic agenesis. Ann Surg 2006;244:505-13.

[14] Section on Surgery and the Committee on Fetus and Newborn. Postdischarge follow-up of infants with congenital diaphragmatic hernia. Pediatrics 2008;121:627-32.

[15] Stevens TP, Wijngaarden E, Ackerman KG, et al. Timing of delivery and survival rates for infants with prenatal diagnoses of congenital diaphragmatic hernia. Pediatrics 2009;123:494-502.

[16] Seetharamaiah R, Younger JG, Bartlett RH, et al. Factors associated with survival in infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: a report from the Congenital Diaphragmatic Hernia Study Group. J Pediatr Surg 2009;44:1315-21.

[17] Tsao K, Allison ND, Harting MT, et al. Congenital diaphragmatic hernia in preterm infant. Surgery 2010;148:404-10.

[18] Kitano Y, Okuyama H, Saito M, et al. Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: a multicenter survey in Japan. Ultrasound Obstet Gynecol 2011;37:277-82.

[19] Usui N, Kitano Y, Okuyama H, et al. Reliability of the lung to thorax transverse area ratio as a predictive parameter in fetuses with congenital diaphragmatic hernia. Pediatr Surg Int 2011;27:39-45.

[20] Okuyama H, Kitano Y, Saito M, et al. The Japanese experience with prenatally diagnosed congenital diaphragmatic hernia based on a multi-institutional review. Pediatr Surg Int 2011;27:373-8.

[21] Usui N, Kitano Y, Okuyama H, et al. Prenatal risk stratification for isolated congenital diaphragmatic hernia: results of a Japanese multicenter study. J Pediatr Surg 2011;46:1873-80.

[22] Migliazza L, Bellan C, Alberti D, et al. Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and presurgical stabilization. J Pediatr Surg 2011:1526-32.

[23] Reiss I, Schaible T, van den Hout L, et al. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium Consensus. Neonatology 2010;98:354-64.

[24] van den Hout L, Tibboel D, Vijfhuize S, et al. The VICI-trial: high frequently oscillation versus conventional mechanical ventilation in newborns with congenital diaphragmatic hernia: an international multicenter randomized controlled trial. BMC Pediatr 2011;11:98.

[25] Lazar DA, Cass DL, Rodriguez MA, et al. Impact of prenatal evaluation and protocol-based perinatal management on congenital diaphragmatic hernia outcomes. J Pediatr Surg 2011;46:808-13.

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CASE REPORT

Repair of congenital diaphragmatic hernias through umbilical skin incisions

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Abstract The use of thoracoscopy and laparoscopy in the treatment of congenital diaphragmatic hernias (CDHs) has been recently reported; however, the use of these procedures still remains controversial due to CO_2 insufflation and limited working space. In addition, because of difficult techniques, it has not been widely accepted. Among CDH patients, mild cases whose lung is not hypoplastic, and not associated with persistent pulmonary hypertension of the neonate (PPHN) often develop small defects in the diaphragm that can be repaired using "direct closure." Because direct closure does not require as wide an operative field as that needed for patch closure, we repaired CDH through umbilical skin windows in two neonates with mild CDH to minimize the wounds. With the creation of additional radical small incisions, the surgeries were successfully performed without any intra- or postoperative complications, and the wounds were cosmetically pleasing. The repair of CDHs through umbilical skin windows is a feasible and useful approach in neonates with mild CDH.

Keywords Congenital diaphragmatic hernia (CDH) · Direct closure · Umbilical skin incision

Introduction

Recently, it has become possible to achieve accurate prenatal assessments of patient severity to provide optimal treatment for individuals with congenital diaphragmatic hernia (CDH). Since 2005, we have applied a new protocol for perinatal care and treatment after birth in fetal CDH patients based on a classification that predicts patient severity using the lung to thorax area ratio (L/T ratio) of the contralateral lung [1]. Total defects in the dorsal diaphragm can be observed in severe CDH patients, thereby ensuring a wide operative field for repair. In contrast, patients with mild CDH often develop small defects in the diaphragm similar to "slits" that can be repaired with direct closure. Because the direct closure method does not require as wide an operative field as that needed for patch closure, we assumed that repair could be achieved in mild CDH patients, even with a comparatively narrow operative field. Kitano et al. [2] described that the patch repair might not be needed in patients whose stomach was located in abdomen through all prenatal period, suggesting that the direct closure can be achieved in such cases. Therefore, a smaller operative field may be adequate for repairing hernias in such patients.

In the past 10 years, a variety of abdominal neonatal surgical diseases have been reported to have been successfully treated through umbilical skin windows [3–5]. Therefore, we repaired CDHs through umbilical skin incisions in two neonates with mild CDH to minimize the wounds.

Indications and procedure

We considered the closure of diaphragmatic hernias with umbilical skin incisions for CDH patients as follows:

1. The patient has an isolated CDH without associated life-threatening anomalies.

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2. The patient's stomach is confirmed to be positioned in the abdominal cavity throughout the prenatal period.
3. The patient's severity of CDH is predicted as "mild" on a prenatal assessment of the lung size (L/T ratio of contralateral lung is greater than 0.13) [1] and confirmed with the absence of PPHN.

In both cases, the skin incision line around the umbilicus and the area separating the subcutaneous tissue were depicted with a transverse incision line reaching the intra-abdominal cavity (Fig. 1a). A 360° circular umbilical skin-fold incision was made together with an additional small radial incision (1 cm) to ensure an adequate operative field. The subcutaneous tissue around the umbilicus was widely dissected above the muscle of the abdominal wall. After mobilizing the umbilical skin window, a laparotomy was made in the left upper abdominal wall. A wound retractor XS (Applied Medical Resources Corp., USA) was inserted through the skin window. The entire length of the intestines was pulled out from the thoracoabdominal cavity and examined for associated abnormalities, and direct closure of the diaphragmatic hernia was performed.

Case reports

Summaries of the two patients who underwent CDH repair using this procedure are herein presented (Table 1).

Case 1

Case 1 involved a female patient born at 38 weeks gestation to a 30-year-old mother. The first fetal ultrasound examination revealed left-sided mild CDH (*L/T* ratio = 0.25). The stomach and liver were located in the abdominal cavity throughout the gestational period. No other anomalies were identified. A roentgenogram obtained after birth confirmed that the stomach was located in the abdominal cavity. The patient's circulatory and respiratory conditions were stable without PPHN; therefore, we performed surgery on the 1st day after birth.

As the diameter of the umbilical ring (1.5 cm) was not sufficiently large to ensure an appropriate operative field, an additional longitudinal 1 cm skin incision was made. The defect in the diaphragm was similar to a "slit" and measured 3 × 1 cm in size (Fig. 1b). The patient's post-operative course was uneventful. The umbilical wound 3 months after surgery is shown in Fig. 1c.

Case 2

Case 2 involved a female patient born at 37 weeks gestation to a 38-year-old mother. The first ultrasound examination revealed left-sided mild CDH (*L/T* ratio = 0.15). The stomach and liver were located in the abdominal cavity throughout the gestational period. No other anomalies were identified. The patient's circulatory and respiratory conditions were stable without PPHN; therefore, we performed surgery on the 1st day after birth.

Similar to Case 1, as the diameter of the umbilical ring was small, we created an additional 1 cm transverse skin incision. The diameter of the wound for the laparotomy was 3.8 cm, which was adequate for CDH repair.

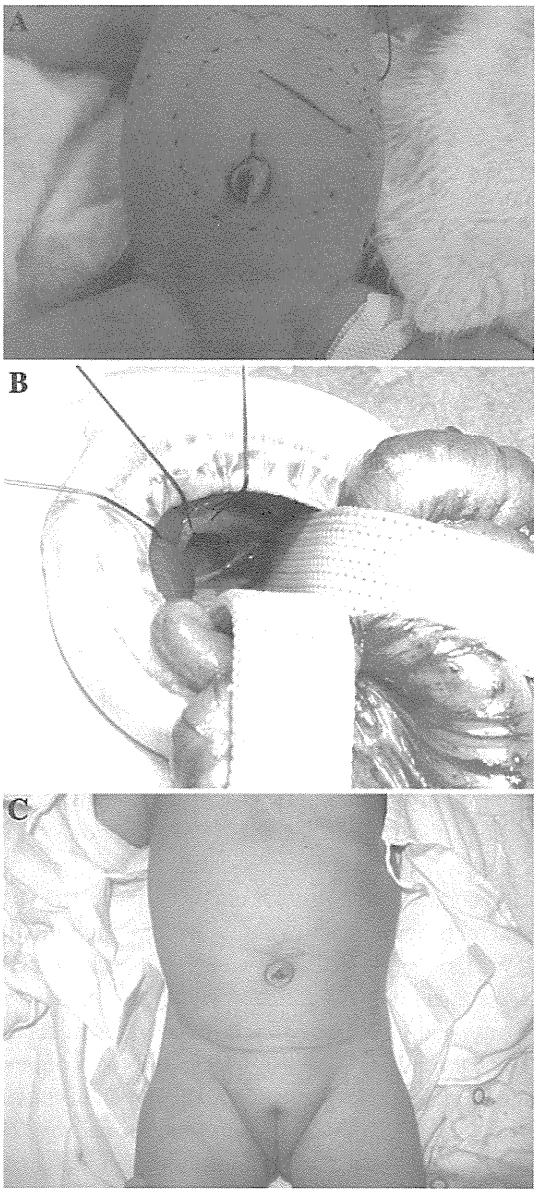

Fig. 1 **a** The skin incision *line* around the umbilicus and the area separating the subcutaneous tissue were depicted with a transverse incision *line* reaching to the intra-abdominal cavity. **b** The umbilical skin window was adequate to achieve direct closure. The defect in the diaphragm in Case 1 measured 3 × 1 cm in size. **c** The umbilical wound 3 months after surgery

Table 1 Summary of the patients, who underwent a CDH repair through the umbilical skin incision

	Case 1	Case 2
Diameter of the umbilical ring (cm)	1.5	1.7
Additional skin incision (cm)	1.0	1.0
Diameter of wound for the laparotomy (cm)	3.5	3.8
Size of defect (cm)	3 × 1	2 × 0.5
Method of the closure	Direct closure	Direct closure
Operation time (min)	139	109
Blood loss (ml)	3	5
Perioperative complications	None	None
Length of hospital stay (days)	21	20

The defect in the diaphragm was a "slit" measuring 2 × 0.5 cm in size that was closed directly. The patient's postoperative course was uneventful.

Discussion

We herein reported that closure of diaphragmatic defects could be achieved through umbilical skin windows in patients with mild CDH.

The mortality rate of infants with severe CDH remains high despite the recent advances in prenatal diagnosis and newly developed therapeutic modalities. Therefore, obtaining an accurate prenatal assessment of patient severity is essential for providing optimal treatment for individuals with CDH. We have previously reported that the lung and thorax transverse area ratio (*L/T* ratio) is an indicator of severity [6, 7] that has been widely used in the assessment of fetal CDH in Japan. Currently, we are using a new protocol of perinatal care and treatment after birth in fetal CDH patients based on a classification of predicted severity determined by the *L/T* ratio [1]. As all fetal CDH patients are in critical condition immediately after birth, they should be managed with extreme care. However, low-risk patients do not require such close management. Severe CDH patients often require patch closure, which necessitates the creation of large incisions due to large defects in the diaphragm. In contrast, most mild CDH patients have smaller defects that can be easily repaired with direct closure. Therefore, we believe that diaphragmatic repair can be achieved in CDH patients, considering the cosmetic aspects.

Kitano et al. [2] reported a multicenter retrospective study of 109 patients with prenatally diagnosed isolated CDH. The described the stomach position was perinatally observed in the abdomen in 20 of 109 left CDH patients, and neither of them needed patch repair. This suggests that stomach position in left CDH patients may be associated with the need for patch repair. This phenomenon is not quite definitive, but we drew on their experience to decide the indications for closure of diaphragmatic hernias through the umbilical skin windows.

Many pediatric surgeons have now begun to utilize the transumbilical approach in the treatment of pediatric surgical disease, especially in neonatal surgery. Odaka first introduced the sliding window method using umbilical incisions in two pediatric patients, who underwent mini-laparotomy to avoid large abdominal incisions [3]. We adapted this method to CDH repair. Because the skin of newborns is stretchable, the wound retractor XS can be inserted through small wounds, providing adequately large surgical fields to perform CDH repair successfully. Even with additional radical skin incisions, the wounds are cosmetically pleasing after surgery, and the operation time is satisfactory with this novel procedure.

Recently, the use of endoscopic surgery in neonates with CDH has been reported. However, there are some problems to be solved. Carbon dioxide insufflation may rapidly worsen the respiratory and hemodynamic conditions of these fragile beings, increasing the blood gas CO_2 levels and creating hypoxemia and pulmonary hypertension. Thoracoscopy technique may not allow for an examination of the intra-abdominal viscera. In addition, the laparoscopic approach may not be able to offer sufficient working space and requires sustained CO_2. Although we have only these two patients and need more patients to compare operative techniques between this umbilical procedure and the thoracoscopic or laparoscopic repair, our procedure allowed for an efficient examination of the viscera, did not require CO_2 insufflation and provided an excellent cosmetic outcome. We have not yet used this technique in severe CDH patients; however, patch repair may be achievable if radical incision is additionally extended.

Our findings suggest that CDH repair through umbilical skin windows is a safe and useful approach for the treatment of neonates with mild CDH.

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