Introduction:

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 2,500 to 5,000 live births.[1-3]_ENREF_1 Infants with CDH experience severe respiratory failure due to pulmonary hypoplasia and pulmonary hypertension of the newborn (PPHN). During the last decade, new supportive modalities and new therapeutic strategies, such as inhalation of nitric oxide (iNO), extracorporeal membrane oxygenation (ECMO), high frequency oscillation ventilation (HFOV), and gentle ventilation strategies with permissive hypercapnia, have been introduced. Such medical advances have improved mortality and morbidity in infants with CDH.

In Japan, the large number of hospitals for neonatal surgery makes centralizing infants with CDH in tertiary centers difficult. Therefore, it is speculated that the therapeutic strategies used to treat CDH might not be standardized and might vary among institutions. The use of different strategies to treat CDH might affect the outcome of the disease. Additionally, recent reports have demonstrated a relationship between outcome and hospital volume in the treatment of CDH [4] as well as a relationship with neonatal intensive care.[5] Because a nationwide survey of CDH has not been conducted in Japan, the effects of the hospital volume-outcome relationship and the effects of different therapeutic strategies used with CDH patients in Japan remain unexplored. The aim of this study was to evaluate the relationships among the number of CDH patients, survival rates, and the current strategies employed at individual hospitals.

Methods:

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

We distributed a questionnaire to 159 educational hospitals for pediatric surgery and/or tertiary perinatal care centers. The study participants included infants with CDH born between 2006 and 2010. One hundred and nine institutes responded. The collection rate was 68.6%. Twenty six institutes had no cases with CDH. Ultimately, 83 institutes with 674 CDH cases were analyzed.

The questionnaire included items regarding the number of patients, the type of CDH (isolated or non-isolated CDH), the number of survivors, the timing of diagnosis (prenatal or postnatal), the delivery mode, and neonatal therapeutic strategies.

Isolated CDH was defined as a case without the occurrence of any life-threatening major anomalies. Survival was defined as "survival to discharge." Vaginal delivery included both spontaneous delivery and induction delivery. Neonatal therapeutic strategies included choosing a ventilator mode, applying the policy of gentle ventilation with permissive hypercapnia, using tolerable levels of blood gas parameters, administering sedation during acute phases, using specific modalities to treat PPHN (iNO, ECMO), and choosing the timing of surgical repair. We classified the hospitals into three groups according to the number of CDH patients treated: Group 1 (G1): more than 21 patients, Group 2 (G2): between 11 and 20 patients, and Group 3 (G3): fewer than 10 patients.

Data were analyzed by using SPSS version 19.0 statistical software (SPSS Inc., Chicago, USA). The statistical analysis was performed using the chi square test, Fisher's exact test for categorized factors, and a logistic regression analysis. Bonferroni's

correction was used as a posthoc test. A p-value < 0.05 was considered to be significant.

The numerical data represent the medians (range).

Results:

The number of hospitals in G1, G2, and G3 were 7, 14, and 62, respectively. Total number of CDH patients was 674. The median (range) number of CDH patients in G1, G2, and G3 were 29 (22-43), 14 (11-17), and 4 (1-10), respectively. The median (range) number of the CDH patients at the individual hospitals was 5 (1-43). The mode value of the CDH patients at the individual hospitals was 4 (Figure).

Timing of diagnosis

The rates of prenatal diagnosis in G1, G2, and G3 were 82.8%, 75.4%, and 60.1%, respectively. The rate of prenatal diagnosis in G3 was significantly lower than that in both G1 and G2 (G1 vs. G3; p<0.001, G2 vs. G3; p=0.003).

Survival rate

The survival rates are shown in Table 1. The overall survival rates for all cases, the cases with a prenatal diagnosis, and the cases with a postnatal diagnosis were 74.5%, 69.8%, and 86.4%, respectively. The overall survival rate for the cases with a prenatal diagnosis was significantly lower than that among the cases with a postnatal diagnosis (p < 0.001).

In all cases, the survival rates in G1, G2, and G3 were 79.5%, 70.2%, and 73.5%, respectively. If the cases were restricted to those with isolated CDH, the survival rate was 82.6%. Compared among the three groups, the survival rates in G1, G2, and G3 were 87.8%, 78.8%, and 81.4%, respectively. The survival rate in G1 was significantly higher compared with that in G2 (p = 0.023).

When only the cases of CDH with a prenatal diagnosis were included, the survival rate was significantly higher in G1 than that in G2 or G3 (78.1% vs. 64.6% vs. 65.2%, G1 vs.G2, p = 0.008; OR: 0.512 [95% CI: 0.313-0.837], G1 vs. G3, p = 0.009; OR: 0.526 [95% CI: 0.325-0.851]). If the cases were restricted to 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: the level of preductal $PaCO_2$ ranged from 50 to 60 mmHg, the level of preductal PaO_2 ranged from 60 to 70 mmHg, the level of preductal SpO_2 ranged from 90% to 95%, and the level of preductal pH ranged from 7.30 to 7.35 (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 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 four postnatal days in most of the hospitals. In almost all of the hospitals in G1, surgery was performed within two postnatal days (Table 4).

The difference in strategies by physicians of different specialties.

In 54 institutes, neonatologists treat CDH infants. In 5 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 a department of neonatology. The attending physicians were pediatric surgeons, pediatric cardiologists, anesthesiologists, obstetricians and of 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 to 93%) and 85% (range: 78 to 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 staffs 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 stuff 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 NICUs. 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 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 literature reports 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 relationship for CDH.[4, 27] The Canadian Pediatric Surgery Network reported a volume-outcome relationship 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 relationship between hospital volume and outcome. In their study, 2,203 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 ($\leq$ 6 cases/year), medium (> 6 and $\leq$ 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 five 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,_ENREF_1[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.

Acknowledgment

This study was partially supported by a grant from the Ministry of Health, Labor and Welfare of Japan.

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, Dzakovic A, Nemes L, Jennings RW, 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, Friberg LG, Heikkinen M, Hurme T, 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, Kuroda S, Ikegami R, Kamiyama M, 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, Matthews JN, Beck J, Sadler C, 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. Journal of Pediatric Surgery. 2004; 39: 821-24.

23   Tracy ET, Mears SE, Smith PB, Danko ME, Diesen DL, Fisher KA, 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, Hop W, Siemer J, van de Ven K, 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, De Klein A, Rottier R, Ijsselstijn H, 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.

Figure legend

The number of CDH cases at the individual hospitals.

The black bar, gray bar, and white bar indicate G1, G2, and G3, respectively.

Table 1. Survival rates

	Total	G1	G2	G3
Total cases				
overall				
n/N	502/674 (74.5%)	171/215 (79.5%)	134/191 (70.2%)[a]	197/268 (73.5%)
OR (95%CI)		1.00	0.605 (0.384-0.952)	0.714 (0.465-1.096)
isolated cases				
n/N	473/572 (82.6%)	159/181 (87.8%)	126/160 (78.8%)[b]	188/231 (81.4%)
OR (95%CI)		1.00	0.513 (0.286-0.920)	0.605 (0.347-1.054)
non-isolated cases				
n/N	29/102 (28.4%)	12/34 (35.3%)	8/31 (25.8%)	9/37 (34.3%)
OR (95%CI)		1.00	0.638 (0.219-1.857)	0.589 (0.211-1.649)
Cases with prenatal diagnosis				
overall				
n/N	337/483 (69.8%)	139/178 (78.1%)	93/144 (64.6%)[c]	105/161 (65.2%)[d]
OR (95%CI)		1.00	0.512 (0.313-0.837)	0.526 (0.325-0.851)
isolated cases				
n/N	318/401 (79.3%)	129/148 (87.2%)	88/117 (75.2%)[e]	101/136 (74.3%)[f]
OR (95%CI)		1.00	0.447 (0.236-0.847)	0.425 (0.230-0.787)
non-isolated cases				
n/N	19/82 (23.2%)	10/30 (33.3%)	5/27 (18.5%)	4/25 (16.0%)
OR (95%CI)		1.00	0.210 (0.133-1.559)	0.149 (0.103-1.414)
Cases with postnatal diagnosis				
overall				
n/N	165/191 (86.4%)	32/37 (86.5%)	41/47 (87.2%)	92/107 (86.0%)
OR (95%CI)		1.00	1.068 (0.299-3.816)	0.958 (0.322-2.848)
isolated cases				
n/N	155/171 (90.6%)	30/33 (90.9%)	38/43 (88.4%)	87/95 (91.6%)
OR (95%CI)		1.00	0.760 (0.168-3.468)	1.087 (0.271-4.367)
non-isolated cases				
n/N	10/20 (50.0%)	2/4 (50.0%)	3/4 (75.0%)	5/12 (41.7%)
OR (95%CI)		1.00	3.000 (0.150-59.890)	0.714 (0.074-6.922)

a; p=0.030, b; p=0.023, c; p=0.008, d; p=0.009, e; p=0.013, f; p=0.007

Table2. Ventilator care

	Total (n=83)		G1 (n=7)		G2 (n=14)		G3 (n=62)		p value
Ventilator mode									0.963
HFOV	67	(80.7%)	6	(85.7%)	11	(78.6%)	50	(80.6%)	
decision depending on the situation	6	(7.2%)	1	(14.3%)	1	(7.1%)	4	(6.5%)	
SIMV	5	(6.0%)	0	(0.0%)	1	(7.1%)	4	(6.5%)	
no treatment principle	2	(2.4%)	0	(0.0%)	0	(0.0%)	2	(3.2%)	
no response	3	(3.6%)	0	(0.0%)	1	(7.1%)	2	(3.2%)	
Gentle ventilation									0.819
applying to all cases	69	(83.1%)	7	(100%)	13	(92.9%)	49	(79.0%)	
decision depending on the situation	4	(4.8%)	0	(100%)	0	(0.0%)	4	(6.5%)	
not applied	2	(2.4%)	0	(0.0%)	0	(0.0%)	2	(3.2%)	
no treatment principle	4	(4.8%)	0	(0.0%)	0	(0.0%)	4	(6.5%)	
no response	4	(4.8%)	0	(0.0%)	1	(7.1%)	3	(4.8%)	
Tolerable level of pre-ductal PCO_2									0.891
<40mmHg	5	(6.0%)	0	(0.0%)	0	(0.0%)	5	(8.1%)	
40mmHg≤ <50mmHg	17	(20.5%)	2	(28.6%)	3	(21.4%)	12	(19.4%)	
50mmHg≤ <60mmHg	36	(43.3%)	3	(42.9%)	8	(57.1%)	25	(40.3%)	
60mmHg≤ <70mmHg	15	(18.1%)	2	(28.6%)	2	(14.3%)	11	(17.7%)	
70mmHg≤	3	(3.6%)	0	(0.0%)	0	(0.0%)	3	(4.8%)	
no response	7	(8.4%)	0	(0.0%)	1	(7.1%)	6	(9.7%)	
Tolerable level of pre-ductal PO_2									0.745
<60mmHg	10	(12.0%)	1	(14.3%)	2	(14.3%)	7	(11.3%)	
60mmHg≤ <70mmHg	25	(30.1%)	3	(42.9%)	5	(35.7%)	17	(27.4%)	
70mmHg≤ <80mmHg	10	(12.0%)	2	(28.6%)	1	(7.1%)	7	(11.3%)	
80mmHg≤ <90mmHg	12	(14.5%)	1	(14.3%)	1	(7.1%)	10	(16.1%)	
90mmHg≤ <100mmHg	7	(8.4%)	0	(0.0%)	0	(0.0%)	7	(11.3%)	
100mmHg≤	5	(6.0%)	0	(0.0%)	1	(7.1%)	4	(6.5%)	
no response	14	(16.9%)	0	(0.0%)	4	(28.6%)	10	(16.1%)	
Tolerable level of pre-ductal SpO_2									0.533
<80%	2	(2.4%)	0	(0.0%)	1	(7.1%)	1	(1.6%)	
80%≤ <90%	22	(24.5%)	2	(28.6%)	5	(35.7%)	15	(24.2%)	
90%≤ <95%	34	(41.0%)	5	(71.4%)	6	(42.9%)	23	(56.5%)	
95%≤ <100%	19	(22.9%)	0	(0.0%)	1	(7.1%)	18	(29.0%)	
100%	1	(1.2%)	0	(0.0%)	0	(0.0%)	1	(1.6%)	
no response	5	(6.0%)	0	(0.0%)	1	(7.1%)	4	(6.5%)	
Tolerable level of pH									0.445
<7.25	7	(8.4%)	0	(0.0%)	1	(7.1%)	6	(9.7%)	

7.25≤ <7.30	18	(21.7%)	1	(14.3%)	3	(21.4%)	14	(22.6%)
7.30≤ <7.35	38	(45.8%)	4	(57.1%)	8	(57.1%)	26	(41.9%)
7.35≤ <7.40	11	(13.3%)	1	(14.3%)	0	(0.0%)	10	(16.1%)
7.40≤ <7.45	2	(2.4%)	0	(0.0%)	0	(0.0%)	2	(3.2%)
7.45≤	2	(2.4%)	1	(14.3%)	1	(7.1%)	0	(0.0%)
no response	5	(6.0%)	0	(0.0%)	1	(7.1%)	4	(6.5%)

Table 3. Sedation treatments used during acute management

	Total (n=83)		G1 (n=7)		G2 (n=14)		G3 (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
acceptable of movability	30	(36.1%)	3	(42.9%)	5	(35.7%)	22	(35.4%)	
untolerability of movability	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%)	

Table 4. The timing of surgical repair

	total (n=83)		G1 (n=7)		G2 (n=14)		G3 (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
Day0	2	(2.4%)	1	(14.3%)	0	(0.0%)	1	(1.6%)	
Day1-2	31	(37.3%)	4	(57.1%)	5	(35.7%)	22	(35.5%)	
Day3-4	37	(44.6%)	1	(14.3%)	6	(42.9%)	30	(48.4%)	
Day5-7	5	(6.0%)	1	(14.3%)	0	(0.0%)	4	(6.5%)	
Day8-	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%)	