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Original Article

Postnatal predictors for outcome in congenital diaphragmatic hernia: A single-center retrospective cohort study from India

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ABSTRACT

Background: Congenital diaphragmatic hernia (CDH) has high morbidity and mortality. Many outcome predictors have been tried. **Objective:** To assess the short-term outcomes of neonates with isolated CDH and find the predictors of outcome. **Methods:** Neonates with isolated CDH managed over 12-year period from June 2004 were analyzed. Antenatal counseling, delayed surgery after stabilization, primary conventional ventilation and rescue high frequency ventilation if needed is the unit protocol. Details on baseline characteristics, delivery room management, clinical details, ventilation details, management of pulmonary hypertension, inhaled nitric oxide usage, operative details, and post-operative period were noted. Oxygenation index (OI) was calculated, and echocardiography findings on pulmonary hypertension were noted. Outcome predictors were assessed. **Results:** 40 neonates with isolated CDH were managed during the study period. The mean birth weight and gestation were 37.7±1.55 weeks and 2830±480 g, respectively. The majority of them were intramural and had an antenatal diagnosis. Definitive sepsis, pneumothorax, and severe pulmonary hypertension were seen in 10, 9, and 17 neonates, respectively. In 32 neonates, surgical repair was done and 31 (78%) survived at discharge. Median (range) of maximum OI on day 1 was 6 (2.2-39) and 59.9 (7.65-96) for survivors and non-survivors, respectively. Area under the curve (AUC) for OI prediction of survival was 0.94 (confidence interval 0.86-0.99). The adjusted odds ratio for survival, when maximum OI was below 15, was 36.2 (4.6-142). Receiver operating curve showed AUC for OI in predicting survival was 0.95 (0.86-0.99). **Conclusion:** We found 78% survival for isolated CDH neonates using standard protocol and OI is a good predictor for survival.

Key words: *Congenital diaphragmatic hernia, Neonate, Survival, Predictors*

Congenital diaphragmatic hernia (CDH) has an incidence of 1 in 2500 live births and left sided postero-lateral defect is the most common type [1]. In the recent decades, outcomes of CDH have improved with advances in the management of pulmonary hypertension, gentle ventilation techniques, and elective surgery after initial stabilization [2]. The reported survival rate has improved from 50% to nearing 85% for CDH, but the scenario is not same in developing countries [3-6]. Standardized guidelines for the management of CDH infants were developed in 2010 by "CDH EURO" consortium and recently updated [7,8].

The outcome of CDH depends on the timing of herniation, position of liver, severity of pulmonary hypoplasia, and associated congenital malformations. Despite the advances in prenatal and neonatal care, the high mortality and morbidity for CDH infants prompt the researchers to study the predictors of outcome in CDH [9]. Antenatal and postnatal predictors for survival in CDH neonates have been suggested and both have the similar prognostic ability [9,10]. Antenatal predictors involve markers for severity of lung hypoplasia and pulmonary hypertension [10]. The score for neonatal acute physiology in first day, CDH study group composite score, Wilford Hall/Santa Rosa prediction formula, and oxygenation index (OI) are some of the postnatal predictors for CDH [9,11-13]. Antenatal predictors do not account for the postnatal adaptation of the baby. Simple predictor scores such as OI have easy bedside application, rather than complicated composite scores [13]. There are only a few studies on CDH from India [5,6].

The present study was conducted to assess the outcome at discharge for neonates diagnosed with CDH within 6 hours of life during the period from June 2004 to June 2016 and to find the postnatal factors predicting their survival.

METHODS

This retrospective cohort study included both term and preterm neonates with antenatal detected CDH or postnatal detected CDH within 6 hours of life and admitted to our tertiary level III neonatal intensive care unit (NICU) during the 12-year period from June 2004 to June 2016. Neonates with other major congenital

malformations and chromosomal abnormalities were excluded. The data regarding the diagnosis of CDH were retrieved from hospital medical record department database using specific coding system and were counter checked with neonatal admission records and pediatric surgery records. Detailed information regarding general characteristic features, clinical parameters, ventilation parameters, surgery details, and duration of hospital stay were collected from the case records. The Ethical Committee approval was obtained.

Unit Protocol in CDH Management

Parents of antenatal detected CDH were counseled by fetal medicine team, neonatal team, and pediatric surgical team. Delivery calls of anticipated CDH were attended by a neonatal team led by senior resident or consultant on call and infants were resuscitated, intubated electively in the delivery room, and transferred to NICU in transport incubator with transport ventilator support. In NICU, both antenatal and postnatal detected CDH were managed in the same way. Synchronized conventional ventilation (Drager Babylog 8000 or SLE2000 or Acutronic neonatal ventilator) was the initial mode, and high frequency (HF) ventilation (Sensormedics 3100A HF oscillatory ventilator) was used as rescue mode if mean airway pressure (MAP) requirement was >12 cm H_2O.

Umbilical venous and arterial lines were accessed within few hours of life. Blood gas analysis was done at least 6 hourly or more frequently till initial stabilization. Bedside chest X-ray was taken. Echocardiography was performed by Pediatric Cardiologist within 24 h of life to rule out cardiac anomaly and to determine pulmonary hypertension. Inhaled nitric oxide (iNO) was given when OI was >20 or nearing 20. Use of sildenafil and inotropes was based on the clinical condition of the neonate and consultant decision. Delayed surgical repair after hemodynamic stabilization is the unit protocol. Neonates with CDH undergo surgery only if FiO_2 requirement <40% on conventional mode and pre-ductal saturation of at least 85% without iNO support and inotropes, lactates <3 mmol/l, and urine output was >1 ml/kg/h. Routine use of sedation or neuromuscular blockers was not practiced. Facilities for HF ventilation and iNO were available from 2004 and 2006, respectively.

General characteristic features regarding antenatal scans, timing of detection of CDH, intramural or extramural, mode of delivery, birth weight, gestational age, Apgar score, presence of associated anomalies, side of defect, and position of liver were collected. Position of the liver was noted as up or down based on findings mentioned in the antenatal scans or from documented peroperative surgical findings [14]. Clinical parameters such as information regarding age at diagnosis, culture proven sepsis, pneumothorax, pulmonary hypertension, and use of iNO, inotropes, and sildenafil, and use of opioids before surgery were collected. Pulmonary hypertension was graded into mild, moderate, and severe based on pressure gradient through ductus arteriosus. Supra-systemic pressure with the right to left shunting were diagnosed as severe, bi-directional shunt as moderate and sub-systemic pressure as mild pulmonary hypertension [15].

Detailed information regarding ventilation such as mode and duration of ventilation, maximum peak inspiratory pressures required, MAP and oxygen requirement was collected. Pre-operative ventilation groups were defined as HF ventilation group, conventional ventilation group, or mixed group. Neonates in whom HF ventilation started within 2 h of life were grouped to HF ventilation group. Neonates in whom conventional ventilation was used till surgery were grouped to conventional ventilation group. Neonates in whom conventional ventilation was initiated and changed to HF ventilation based on clinical situation or *vice versa* were grouped into mixed ventilation group. OI is calculated from blood gas drawn from umbilical arterial blood sample [16]. Maximum OI on day 1, day 2, and day 3 of life was taken for analysis.

Details regarding age at surgery, operative findings, post-operative complications, and duration of hospital stay were collected from the neonates who underwent surgical repair for CDH. Final outcomes were classified as survivors and non-survivors at discharge. Severity of pulmonary hypertension and OI cut-off of 15 were analyzed for predictors of survival [9,17].

Statistics

Statistical analysis was done using SPSS for Windows Version 16.0 (Chicago). General characteristics, ventilation, and clinical details were compared between survivors and non-survivors. For comparison of categorical variables, Chi-square test and Fisher's exact test were used. For comparison of continuous variables, t-test and Mann–Whitney test were used. Odds ratio (OR) was calculated, and regression analysis was used to find adjusted OR (aOR). Receiver operating curve (ROC) and Youden's index (highest sum of sensitivity and specificity point) were used to find the cut-off for continuous variable OI in predicting the survival.

RESULTS

During the study period, 43 neonates detected with CDH were admitted to our NICU within 6 h of life. Among 43 neonates, 1 had Fryns syndrome, and 2 infants were discharged against medical advice. Thus, 40 neonates with CDH were included in the study as shown in study flow chart (Fig. 1).

The mean gestational age at birth and birth weight of neonates with CDH was 37.7±1.6 weeks and 2830±480 g, respectively. All infants had left sided CDH and 80% (33 neonates) had antenatal diagnosis of CDH. The baseline characteristics are shown in Table 1. The smallest neonate in the study weighed 1.16 kg and underwent repair. The birth weight and gestational age of survivors were significantly higher compared to non-survivors. Position of the liver was available in 25 neonates, and the liver-up position was similar in survivors and non-survivors. Among neonates with sepsis, *Klebsiella* sp. was the most common organism (n4), followed by *Acinetobacter* (n2), *Enterobacter* (n2) and *Staphylococcal aureus* (n1) and *Candida albicans* (n1).

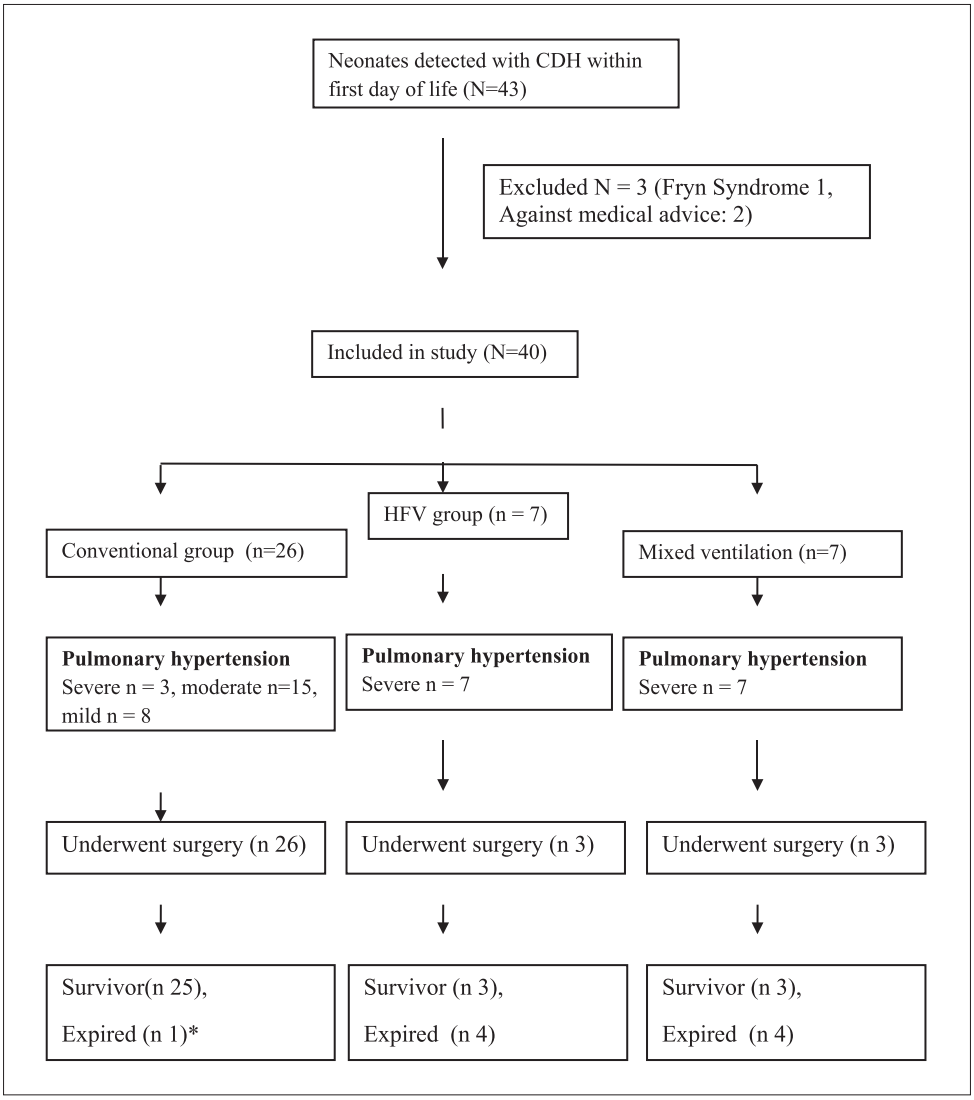

Figure 1: Study flow chart. HFV group: High-frequency ventilation group. *Preterm neonate 1160 g, had severe pulmonary hypertension

Infections occurred mostly in post-operative hospital stay (n=9, 22.5%).

Pre-operative pneumothorax was seen in 9 neonates (22.5%) and pneumothorax was ipsilateral in 2 neonates. All the non-survivors had severe pulmonary hypertension, whereas only 25% (8 neonates) of the survivors had severe pulmonary hypertension (Table 1). The details of inotropes are as follows: Dopamine alone (n=1, baby had early onset *Klebsiella* sepsis), both dopamine and dobutamine (n=6, 15%), both milrinone and dobutamine (n=12, 30%). The median (range) OI among the neonates, prior starting iNO (n=17, 42.5%) was 18.7 (7.8-56) and response to iNO was seen in 14 neonates. Sildenafil alone was used in 4 neonates during the pre-operative period, and all of them survived.

The details various ventilation groups in the study are shown in Fig. 1. Survival was better in conventional group (96%, 25 neonates) when compared to HF ventilation (43%, 3 neonates) or mixed ventilation groups (43%, 3 neonates), and severe pulmonary hypertension was seen in all neonates in HF ventilation and mixed ventilation groups.

MAP, FiO_2, and OI requirement were significantly higher in non-survivors (Table 2). Maximum OI was similar in antenatal and postnatal detected CDH neonates 7.6 (2.1-96.7) and 8 (3.6-68), respectively. All the neonates with maximum OI on first day <7.5 survived (16 neonates) while those with maximum OI on first day >45 (7 neonates) did not survive. Maximum OI predicted the survival and ROC curve showed area under the curve (AUC) was 0.946 (CI 0.86-0.99). Youden's statistic index showed the best cut-off of OI was 17 for predicting survival in neonates with CDH (Fig. 2).

CDH surgical repair was done in 32 neonates (80%) and elective repair was done in 31 neonates, but 1 neonate had to undergo emergency repair for gastric volvulus. The median age at surgical repair for the management of CDH was 3.5 days (range 2-12 days). The median duration of post-operative ventilation and hospital stay was 2.5 (range 1-15) days and 20.5 (range 8-45), respectively. The only post-operative mortality was a preterm neonate with birth weight 1.16 kg on the 45th post-operative day due to necrotizing enterocolitis. Chylous ascites occurred in 1 neonate at the third week of life postoperatively and it resolved by conservative management. Supplemental oxygen requirement at 28 days of life was seen in one neonate and at discharge no neonate required supplemental oxygen.

Table 1: Baseline characteristics

General characteristics	Survivors (n=31)	Non-survivors (n=9)	p value
Gestational age at birth* Mean (SD) weeks	38 (1.11)	36.8 (2.4)	0.03
Birth weight† Median (range) kg	3.00 (2.06-3.6)	2.29 (1.16-3.3)	0.013
Apgar score at 5 min* Median (range)	6 (5-9)	6 (5-8)	0.47
Boy§ n (%)	21 (67.8)	6 (66.7)	0.62
In-born§ n (%)	27 (87)	7 (77.8)	0.41
Preterm (<37 weeks)§ n (%)	04 (13)	3 (33.3)	0.32
Birth weight >2500 g§ n (%)	29 (93.5)	4 (44.4)	0.003
Antenatal diagnosed§ n (%)	26 (84)	7 (77.8)	0.90
Delivery by section§ n (%)	17 (54.8)	7 (77.7)	0.20
Liver up** (n=25)† n/N	8/21	3/4	0.20
Sepsis§ n (%)	9 (29)	1 (11)	0.40
Pneumothorax§ n (%)	4 (12.9)	5 (55.5)	0.02
Requirement of inotropes§ n (%)	14 (45.2)	9 (100)	<0.01
Severity of pulmonary hypertension§			
Mild n (%)	15 (48.4)	0	<0.01
Moderate n (%)	8 (25.8)	0	
Severe n (%)	8 (25.8)	9 (100%)	
Requirement of iNO§ n (%)	8 (25.8)	9 (100)	<0.01

*t-test, †Mann–Whitney test, §Fisher exact test, **Data were available only in 25 infants. iNO: Inhaled nitric oxide, SD: Standard deviation

Table 2: Ventilation details

Variable	Survivors (n=31)	Non-survivors (n=9)	p value
Max OI on first day,† median (range)	6 (2.2-39)	59.9 (7.65-96)	<0.01
Max OI on day 2, median (range)	4.9 (2-25)	37** (8.8-56)	<0.01
Max OI on day 3, median (range)	5.6 (1.7-18)	36** (4-60)	<0.01
Max FiO_2 needed on first day,† median (range)	0.45 (0.21-1)	1 (0.5-1)	<0.01
Max MAP required on first day,* Mean (SD)	11.18 (2.21)	18.33 (3.4)	<0.01

*t-test, †Mann–Whitney test, **n=5 in view 4 infants expired on first day. iNO: Inhaled nitric oxide, Max: Maximum, OI: Oxygenation index, FiO_2: Fractional inspired oxygen, MAP: Mean airway pressure, SD: Standard deviation

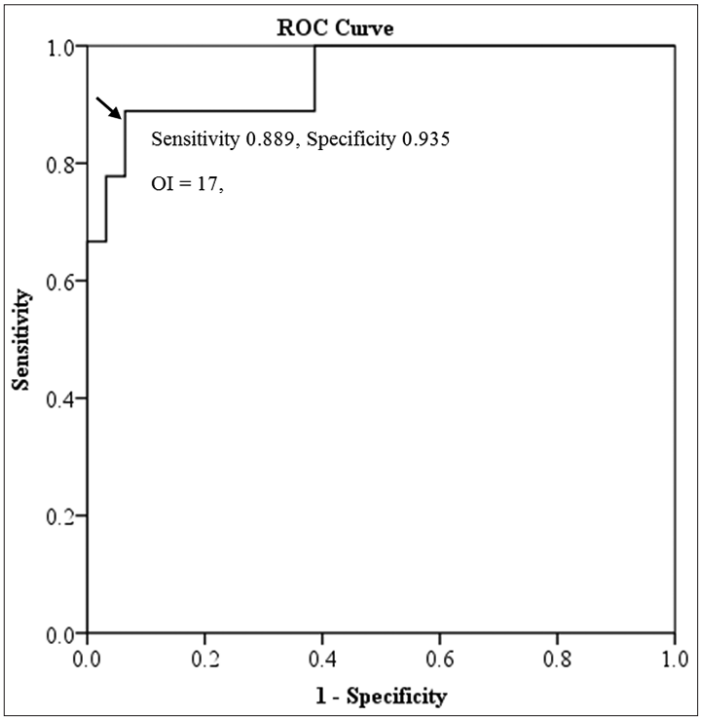

Figure 2: Receiver operating curve: Continuous variable maximum oxygenation index first day and survival

The survival at discharge for CDH was 78% (31 neonates). Among the 9 deaths, 4 died on the first day of life. We analyzed the absence of severe pulmonary hypertension, maximum OI on first day <15, and absence of pneumothorax for predictors of survival (Table 3). The birth weight and gestation aOR showed only maximum OI <15 predicted the survival for CDH neonates. The sensitivity and specificity for maximum OI <15 on first day, to predict survival was 0.89 (confidence interval 0.52-0.99) and 0.90 (84-0.99), respectively. The chances of antenatal detection and survival of CDH infants were similar for neonates with CDH born before or after June 2010.

DISCUSSION

The present single-center study of isolated CDH managed over a period of 12-year, without extracorporeal membrane oxygenation (ECMO) showed survival at discharge was 78%. Similarly, Panda et al. reported survival of 61% for post-operative CDH neonates (n=70) and survival was 90% when sac was present [6]. Jain et al. reported survival of 87.5% for CDH, but many infants presented after 1 week of life in their study [18]. Other studies from developing countries have shown the survival of 50%-65% for antenatal and postnatal detected CDH neonates [4-6,19]. Recent

Table 3: Predictors of survival in CDH

Clinical predictor	Survivors (n=31) (%)	Non-survivors (n=9) (%)	OR (CI)	aOR* (CI)	p value
Maximum OI on first day <15 n (%)	28 (90.3)	1 (11.1)	54 (5.2-255)	36.2 (4.6-142)	<0.01
Absence of severe pulmonary hypertension	23 (74.2)	0	2.1 (1.28-3.5)	1.42 (0.86-3.9)	0.04
Absence of pneumothorax	27 (87)	4 (44.5)	1.96 (0.93-4.1)	1.26 (0.52-10)	0.24

***Adjusted for gestational age and birth weight. OI: Oxygenation index, OR: Odds ratio, PHT: Pulmonary hypertension, aOR: Adjusted odds ratio, CDH: Congenital diaphragmatic hernia, CI: Confidence interval**

studies from developed countries have shown improved survival for isolated CDH to 85-90%, which involves the implementation of protocols, aggressive methods of pulmonary hypertension management, huge monetary support and may be availability of ECMO [20-23].

Once the antenatal diagnosis of CDH is made, assessment of disease severity by scans and postnatal management in an experienced tertiary center has been suggested by CDH EURO consensus to improve the CDH outcomes [8]. In our study, there was no significant difference in survival at discharge between antenatally and postnatally detected CDH. Prenatal detection of CDH and earlier the detection in antenatal period is associated with increased mortality but not reported in all studies [1,24,25]. Burgos et al. found a higher survival in postnatally detected CDH compared to antenatally detected CDH, whereas Lazar et al. reported similar survival [1,25]. In both the studies, severity of CDH as defined liver herniation, need for ECMO and patch repair was higher in antenatally detected CDH infants. In our study, the severity of CDH defined by maximum OI was similar. Antenatal lung indices were not available.

In our study, we found 71% (5 neonates) mortality in low birth weight infants with CDH. Prematurity, low birth weight and small for gestation are risk factors for higher mortality and morbidity in CDH infants [9,26-28]. Grover et al. reported 50% mortality for preterm neonates with CDH (<34 weeks or birth weight <2000 g), compared to 27% mortality for neonates >34 weeks [26]. The mean gestational at delivery in the present study was 37.7±1.6 weeks. Even though CDH consensus suggests delivery should be planned after 39 weeks, Canadian network reported that survival was comparable across gestations from 37 to 40 weeks [29].

Pneumothorax in CDH is related to lung injury and severity of lung hypoplasia. In our study, pneumothorax was seen in 22% (9 neonates) and survival was similar in CDH neonates with or without pneumothorax. Usui et al. reported 14% incidence of pneumothorax among 510 neonates with CDH with gentle ventilation strategies and pneumothorax was associated with poor survival [30]. In our study, mortality was higher in neonates in HF ventilation group compared to the conventional group, but all neonates in HF group had severe pulmonary hypertension. Even recent trial showed no specific advantage of early HF ventilation and almost 50% of CDH infants either died or had chronic lung disease [31].

Many antenatal, postnatal predictors, and scores for CDH are available, but the limitation is that applicability of these predictors at bedside is difficult. The antenatal scores do not account for the postnatal cardio-respiratory adaptation after birth, and postnatal composite score requires complex calculations. Wilford Hall/Santa Rosa prediction formula was suggested using postnatal highest arterial oxygen and carbon dioxide levels on day 1, had a positive predictive value of 83% and AUC of 0.87 in as study by Schultz et al. [13]. OI is widely used in neonates to evaluate the need for ECMO and iNO and is a marker of cardio-respiratory function of neonate [16]. Studies have shown OI is a good predictor in CDH [12,17,32-34].

We found maximum OI on the first day of life as a good predictor of survival in CDH neonates and the AUC for maximum OI on the first day to predict survival at discharge was 0.946. Similarly, Ruttenstock et al. reported AUC for best OI on day 1 to predict survival at 28 days was 0.91 (0.85-0.96) [12]. We report a sensitivity of 0.89 and specificity of 0.90 at a cut-off of 15 for maximum OI on day 1 to predict survival. In similar study from Poland, authors report sensitivity and specificity of 0.94 and 0.88 at cut-off of 12 for OI on first day [17]. Even in the recent trail on the fetal procedure for CDH, Ali et al. found that the lowest OI on day 1 predicted survival in both the groups [32]. Tan et al. suggested serial OI may best predict the survival rather than single best OI in their study among 24 CDH neonates [34]. The presence of severe pulmonary hypertension and persistence of pulmonary hypertension do also predict the short-term mortality and morbidity [9,35]. However, in our study, the aOR for survival in the presence of severe pulmonary hypertension was not statistically significant.

The merit of the study was use of standard protocol for CDH and taking into account, the various parameters affecting survival of neonates with CDH. The limitations of the study are that in view retrospective study antenatal markers of severity, such as liver up position and lung-head ratio, were not available in many case records and operative findings such as presence or absence of sac could not be collected. The ROC curve generated is not smooth and shows need for larger number of neonates with CDH. There is still a gap in evidence-based practice for CDH, and further studies are needed.

CONCLUSION

To conclude, we found a survival of 78% in isolated CDH neonates using the standard protocol in management and maximum OI on day 1 is a good predictor for survival. CDH neonates with maximum OI <15 on day 1 is a good prognostic factor.

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