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Research Article

Is ECMO Dispensable? Outcome of Newborns with CDH - A Single Center Experience and Review of Literature

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Abstract

Objective: Congenital diaphragmatic hernia (CDH) may lead to cardio-respiratory distress in affected newborns and can be incompatible with life. Extracorporeal membrane oxygenation (ECMO) is supposed to improve survival of infants who cannot be managed with conventional therapy. Aim of our study was to investigate outcome of our CDH patients and to compare it to data in literature.

Patients and Methods: 30 patients with perinatally diagnosed CDH were hospitalized at our institution from 1999 - 2017. 3 patients were excluded due to severe comorbidities and redirection of care or failed resuscitation respectively. We divided patients into two groups: Group A included all patients who fulfilled ECMO-criteria (n = 8) and group B included those who did not fulfil any ECMO-criteria (n = 19). All our patients were treated without ECMO.

Results: Patients in group A had significantly larger defects (p = 0.0104), liver herniation was found more frequently (p = 0.038) and three patients suffer from relevant long-term morbidity (p = 0.009). The overall survival of newborns with CDH (n = 30) was 83%. Survival of patients in group A was 75% and in group B was 100%.

Conclusion: Until today the benefit of ECMO to improve survival of newborns with CDH could not be proven. Survival rates of our patients fulfilling ECMO-criteria who were managed with conventional therapy only are not inferior to those treated with ECMO published in literature. We therefore conclude that the necessity and indication for ECMO in patients with CDH has to be questioned more critically.

Keywords: *CDH; ECMO; Survival; Newborns*

Abbreviations

CDH: Congenital Diaphragmatic Hernia; CMV: Conventional Mechanical Ventilation; CLD: Chronic Lung Disease; ECMO: Extracorporeal Membrane Oxygenation; FETO: Fetal Tracheal Occlusion; GA: Gestational Age; GER: Gastro-Esophageal Reflux; HFOV: High Frequency Oscillation Ventilation; MAP: Mean Airway Pressure; O/E LHR: Observed/Expected Lung to Head Ratio; OI: Oxygenation Index; PEG: Percutaneous Endoscopic Gastrostomy; PEJ: Percutaneous Endoscopic Jejeunostomy; PPHN: Persistent Pulmonary Hypertension

Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm that may lead to respiratory distress of affected newborns and is associated with a variable degree of pulmonary hypoplasia and persistent pulmonary hypertension (PPHN). Its prevalence is estimated to be 1 - 4/10.000 live births, although in addition, there is a high suspected rate of stillborn fetuses with CDH [1]. Most defects are located posterolateral on the left side, whereas also right-sided or even bilateral CDH occur [2]. Today CDH is mostly detected in prenatal ultrasound but there are still newborns that present after birth with respiratory distress and consecutively are diagnosed lately [2]. When CDH is detected after the newborn period, defect sizes tend to be smaller and the clinical course and symptoms are much more benign than in patients with perinatally detected CDH, respectively [2]. Isolated CDH accounts for 70% of newborns with CDH. The remaining 30% of patients present with other malformations such as pulmonary, cardiovascular or neurological abnormalities, respectively. Up to 10% of those cases are associated with chromosomal aberrations, genetic syndromes or microdeletions [1]. Despite significant advances in the postnatal management its mortality remains high, mostly ranging from 20 to 30% [1,17,23,24,30-33]. Prematurity, the presence of associated malformations and an early diagnosis are important prognostic factors [3-6]. Furthermore, it could be shown that size of the defect, laterality, liver herniation and observed/expected lung to head ratio (O/E LHR) also have an impact on patient's outcome [7-12]. A standardized postnatal management is crucial to improve patients' outcome and to decrease mortality rates [13,14]. Progression of conventional intensive care including ventilation strategies such as high-frequency oscillation ventilation (HFOV) as well as the use of inhalative nitric oxide (iNO) and others vasodilators as well as preoperative stabilization and delayed surgery did improve outcome over the last decades [15]. Furthermore, prenatal interventions such as fetal tracheal occlusion (FETO) aim to improve lung growth and lung maturity and consecutively the survival rates of newborns with CDH. Up to now studies failed to prove evidence to support FETO and results of current randomized controlled studies are still pending [16]. ECMO is considered for infants who cannot be managed with maximal conventional therapy and is therefore supposed to improve survival rates of these patients [17-20]. Sufficient evidence of randomized controlled trials to prove the efficacy of ECMO are lacking so far. Aim of our investigation was to question the need for ECMO in newborns with CDH.

Material and Methods

Patient population and study design

From 1999 - 2017 35 patients with congenital diaphragmatic hernia were admitted in our institution, which is characterized as a level III neonatal center without availability of ECMO or fetal surgery. Five patients were excluded as diagnosis was made after the neonatal period. Of those diagnosed prenatally or directly after birth (n = 30) three patients were excluded due to severe associated comorbidities and redirection of care or failed resuscitation respectively (Figure 1). One patient had trisomy 18 and severe lung hypoplasia, redirection of care was performed on day 1. Another patient was born with a complex neural crest disorder with caudal regression syndrome and redirection of care was performed on day 4. The third patient had bilateral agenesis of diaphragm with bilateral liver herniation and severe lung hypoplasia, resuscitation failed already in the delivery room.

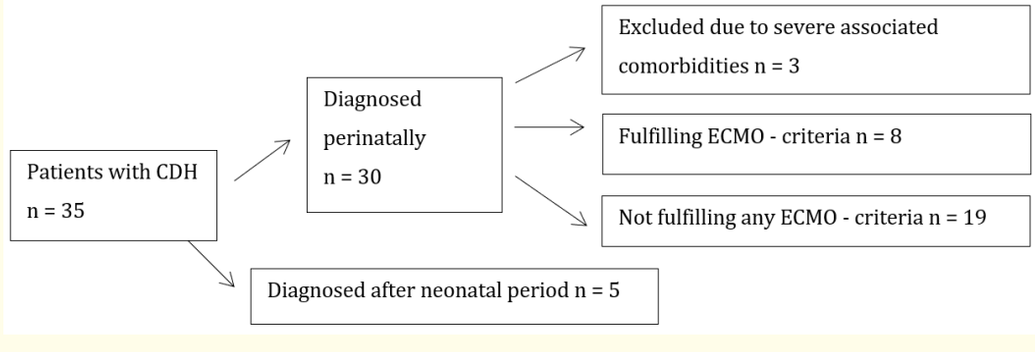

Figure 1: *Flow chart of patient enrollment.*

We stratified patients into 2 groups: Group A (n = 8) included all patients who fulfilled inclusion criteria for ECMO treatment. Two newborns suffered from relevant comorbidities, one of them presented with a persistent atrial septal defect, another one had a deletion syndrome as well as a complete atrioventricular channel. Therefore, they would have probably met exclusion criteria for ECMO treatment, but were still included in our analysis. In both patients the cardiac defects were surgically corrected within the first months of life. Group B (n = 19) included all other patients who did not fulfill criteria for ECMO (Figure 1). ECMO criteria were defined according to the CDH EURO Consortium Consensus [13] (Table 1). All our patients were treated without ECMO. We performed a retrospective chart review of patients' data and compared the two groups in terms of their clinical/birth characteristics, ventilation values, surgical data and outcomes. Median follow up was 7 years (range 6 months - 12 years and 7 months). Primary outcome was survival at hospital discharge. Up to now none of our patients died during follow up, thus overall survival is considered to be equivalent to survival at discharge. IRB-approval was obtained.

• Inability to maintain preductal saturations < 85% or postductal saturations > 70%
• Increased $paCO_2$ and respiratory acidosis with pH < 7.15 despite optimization of ventilatory management
• Peak inspiratory pressure > 28 cmH_2O or mean airway pressure > 17 cmH_2O is required to achieve saturation > 85%
• Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥ 5 mmol/l and pH <7.15
• Systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output <0.5 ml/kg/h for at least 12 - 24h
• Oxygenation index (MAP^1 x $FiO2^2$ x 100/$PaO2^3$) ≥ 40 consistently present

Table 1: *Current ECMO criteria according to the CDH Euro Consortium consensus 2010 [13].*

Study variables

Newborns' clinical characteristics included: gender, birth weight, gestational age, APGAR's score at 5', umbilical arterial pH, side of defect and liver herniation, observed/expected lung to head ratio (O/E LHR), prenatal diagnosis, inborn/outborn and delivery mode. Furthermore we evaluated ventilation data (duration of conventional mechanical ventilation (CMV) and high-frequency oscillation ventilation (HFOV), max. pCO_2, Oxygenation Index (OI), max. FiO_2, max. mean airway pressure (MAP), min. paO_2, min. pH, max. Lactate), required vasodilators as well as timing and mode of surgical repair, size of the defect and whether a patch was used or primary closure of the defect could be achieved. Primary outcome was survival at hospital discharge. As secondary outcomes variables we assessed the following: total duration of mechanical ventilation (CMV/HFOV), length of hospital stay (LOS), postoperative complications such as patch infection, chylothorax/chylaskos and early recurrence (< 6 months) as well as long term sequelae such as spinal/chest wall abnormalities, gastroesophageal reflux (GER), dependence of percutaneous gastrostomy/jejunostomy (PEG/PEJ) tube feeding, chronic lung disease (CLD), late recurrence (> 6 months) and neurodevelopmental delay.

Data analysis

Data of group A and group B were analysed and compared, results are described as absolute values with median and range (minimum - maximum) or as percentages (%). Continuous variables were compared using the Wilcoxon rank sum test and categorical variables were compared using Fishers exact test as appropriate. Statistical analyses were performed using Stata (Version 15.1, StataCorp, College Station, Texas, USA). A level of significance of 0.05 was adopted.

Results and Discussion

Results

In table 2 demographic and clinical characteristics of all patients are shown. Out of 27 newborns with CDH 16 were male and 11 were female. Median birth weight was 3120g and median gestational age was 38 4/7 weeks. 5 new-borns were premature (< 37 weeks GA) and 3 were low birth weight infants (< 2500g birth weight). Mode of delivery was caesarean section in 15 cases. Median APGAR's score at 5' was 6.5 (although score is missing in 6 patients) and median umbilical arterial pH was 7.28. There were no significant differences in the characteristics mentioned above, but in group A there were more right sided defects (p = 0.065) and liver herniation was more frequent

in this group (p = 0.038). Less than half of the cases were diagnosed in prenatal ultrasound, all other patients presented after birth with respiratory distress and were diagnosed late. Median observed/expected lung to head ratio of prenatally identified patients was 34% (group A: 27%, group B: 40%, p = 0.0167), data of three patients could not be obtained. 17 out of 27 patients were inborn and 10 newborns were transferred to our institution after birth (Table 2). Fetal endotracheal occlusion (FETO) was performed in one patient from 30 4/7 to 34 2/7 weeks of gestation in another institution.

	Group A (n = 8)	Group B (n = 19)	Total (n = 27)	p-value
Birth weight(g)	3035 (2100 - 3500)	3210 (2485 - 3860)	3120 (2100 - 3860)	0.276
Gestational age (wk)	38 4/7 (35 - 40 2/7)	38 4/7 (34 5/7 - 40 5/7)	38 4/7 (34 5/7 - 40 5/7)	0.979
5' APGAR	2 (2 - 7)	7 (1 - 10)	6.5 (1 - 10)	0.089
Umbilical arterial pH	7.26 (7.19 - 7.39)	7.28 (7.17 - 7.39)	7.28 (7.17 - 7.39)	0.676
Right sided defect	3 (38%)	1 (5%)	4 (15%)	0.065
Liver herniation	7 (88%)	8 (42%)	15 (55%)	0.038
O/E LHR (%) (n = 10)	27 % (n = 3)	40 % (n = 7)	34 % (n = 10)	0.0167
Prenatal diagnosis	4 (50%)	9 (47%)	13 (48%)	0.615
Inborn	5 (63%)	12 (63%)	17 (63%)	0.651
Caesarean section	6 (75%)	9 (47%)	15 (55%)	0.236

Table 2: *Demographic and clinical data of newborns.*

Median age of patients undergoing surgery was 6 days, surgery was significantly earlier performed in group B compared to group A (p = 0.0086). 3 cases were performed thoracoscopically. Defect size was evaluated intraoperatively based on a standardized classification scheme of the congenital diaphragmatic hernia study group; defects were coded from A to D according to Lally., *et al* [7]. "A" defects were entirely surrounded by muscle, "B" defects had a small (< 50%) and "C" defects had a large (> 50%) portion of the chest wall devoid of diaphragm tissue. Patients with a "D" size defect had complete or near complete absence of the diaphragm [7]. Size of the diaphragmatic defect was B in 14 patients, C in 7 patients and D in 4 patients. None of the perinatally diagnosed patients had an "A" size defect. Size of the defect was significantly larger in group A (p = 0.0104). All "B" defects were closed primarily, whereas all patients with a "C" and "D" defect underwent patch repair (p = 0.039) (Table 3).

	Group A (n = 6)	Group B (n = 19)	Total (n = 25)	p-value
Day of life (DOL)	9 (5 - 35)	4 (1 - 13)	6 (1 - 35)	0.0086
Defect size	B = 1 C = 2 D = 3	B = 13 C = 5 D = 1	B = 14 C = 7 D = 4	0.0104
Patch	5 (83%)	6 (32%)	11 (44%)	0.039
Thoracoscopic surgery	-	3 (16%)	3 (12%)	0.421

Table 3: *Surgical data.*

Median time of conventional ventilation was similar in both groups (p = 0.9745). It is important to note that mean duration of CMV differs strongly between the two groups (mean CMV duration group A: 35 days, mean CMV duration group B: 13 days) which is the result of two statistical outliers with long duration of CMV and a wide range of conventional ventilation days in group A. All patients in group A required HFOV whereas 8 of 19 patients in group B were able to be managed with conventional mechanical ventilation. Median HFOV duration was significantly longer in group A compared to group B (p = 0.0012). According to the CDH EURO Consortium Consensus we assessed ECMO-indications for all patients and therefore evaluated the oxygenation index (OI) based on highest mean airway pressure (MAP), highest FiO_2 and worst paO_2 (OI = MAP x FiO_2 x 100/PaO_2) [13]. Median oxygenation index was 48.95 in group A and 7.7 in group B. All patients in group A had an OI > 40. Furthermore, three patients fulfilled a second ECMO-criterion as they showed respiratory acidosis with a pH < 7.15 and an elevated $paCO_2$. Two patients additionally had a metabolic acidosis with an elevated lactate and increased pH and therefore fulfilled a third ECMO-criterion [13] (Table 4).

	Group A (n = 8)	Group B (n = 19)	Total (n = 27)	p - value
Duration of conventional mechanical ventilation (CMV) (n = 6)	12 days (3 - 118)	11 days (5 - 25)	11 days (3 - 118)	0.9745
Duration of high frequency oscillation ventilation (HFOV) (n = 6)	16 days (5 - 37)	2 days (0 - 18)	4 days (0 - 37)	0.0012
pCO_2 (kPa) (maximum)	11.25 (8.5 - 17.4)	8.9 (6.4 - 16.1)	9.08 (6.4 - 17.4)	0.0435
Oxygenation index (OI)	48.95 (40.5 - 200)	7.7 (1.8 - 30)	16 (1.8 - 200)	0.0001
- FiO_2 (%) (maximum)	100 (100 - 100)	45 (21 - 100)	80 (21 - 100)	0.0004
- MAP (mmHg) (maximum)	11.25 (10.13 - 15)	8.25 (6 - 12)	9 (6 - 15)	0.0018
- paO_2 (mmHg) (minimum)	21.8 (7.5 - 31.5)	54 (27.8 - 85.5)	36.8 (7.5 - 85.5)	0.0001
pH (minimum)	7.12 (6.91 - 7.22)	7.25 (7.15 - 7.35)	7.22 (6.91 - 7.35)	0.0020
Lactate (mmol/l) (maximum)	4.5 (3 - 21)	1.5 (1 - 8.2)	2.2 (1 - 28)	0.0016

Table 4: *Ventilation data.*

All patients in group A required inhalative NO in contrast to 8 out of 19 patients in group B (42%) who did not require vasodilators at all (p = 0.034). Furthermore, 7 patients in group A (88%) required phosphodiesterase inhibitors additionally (p = 0.021) and half of those patients required additional prostaglandins (p = 0.149).

Primary outcome was survival at hospital discharge. Survival of all newborns with CDH that were admitted in our institution (n = 30) was 83%. Overall survival of enrolled patients (n = 27) was 93% (group A:75%, group B: 100%, p = 0.08). Out of 30 newborns, 5 patients suffer from major comorbidities (17%) and 25 patients had isolated CDH (83%). Survival of patients with isolated CDH was 92% (group A: 75%, group B: 100%, p = 0.05). Furthermore, all patients who underwent surgical repair survived. Median duration of total mechanical ventilation (CMV and HFOV) was 36 days in group A and 14 days in group B (p = 0.015). Patients in group A stayed significantly longer in hospital than patients in group B (p = 0.008). We evaluated postoperative complications such as patch infection, chylothorax/chylaskos and early recurrence, which is defined as recurrence occurring less than 6 months postoperatively. Recurrent hernia occurred in 24% of patients (p = 0.125). All of these patients underwent a patch repair, thus they all had large defects (size C or D); one of the patients suffered from recurrent hernia because of a patch infection. There was no significant difference in the prevalence of postoperative complications between both groups. Long-term sequelae were defined as relevant morbidity that would require permanent treatment or interdisciplinary support such as medical or surgical therapy or physiotherapy and would persist after the first six months of life in affected infants. Spinal or chest wall deformations were found in almost one third of our patients during long-term follow-up without necessity of surgical intervention so far (Table 5).

	Group A (n = 6)	Group B (n = 19)	Total (n = 25)	p-value
Total duration of mechanical ventilation (CMV and HFOV)	36 days (10 - 155)	14 days (5 - 43)	21 days (5 - 155)	0.015
Length of hospital stay (LOS)	133 days (35 - 278)	37 days (20 - 94)	45 days (20 - 278)	0.008
Postoperative complications				
Patch infection	1 (17%)	-	1 (4%)	0.240
Chylothorax/chylaskos	2 (33%)	3 (16%)	5 (20%)	0.343
Early recurrence (< 6 months)	3 (50%)	3 (16%)	6 (24%)	0.125
Long-term sequelae				
Spinal/chest wall abnormalities	3 (50%)	5 (26%)	8 (32%)	0.274
Gastro-esophageal reflux (GER)	4 (67%) Fundoplication: 3(50%)	7 (37%)	11(44%)	0.209
Dependence of PEG-/PEJ- tube feeding	3 (50%)	-	3 (12%)	0.009
Chronic lung disease with long-term oxygen requirement	3 (50%)	-	3 (12%)	0.009
Late recurrence (> 6 months)	1 (17%)	-	1 (4%)	0.240
Neurodevelopmental delay	3 (50%)	-	3 (12%)	0.009

Table 5: *Secondary outcome variables of all patients with surgical repair (n = 25).*

We investigated the prevalence of gastrointestinal difficulties such as gastro-esophageal reflux (GER) and accompanying failure to thrive in our cohort. 11 infants suffer from clinical GER (44%), three patients underwent fundoplication subsequently. In three out of twenty-five patients relevant long-term morbidities are present, they all belong to group A ($p = 0.009$). All three patients suffer from chronic lung disease with two of them requiring home oxygen therapy and gastro-esophageal reflux with (transient) PEG-/PEJ tube feeding, respectively. Furthermore, a recurrence occurred in two of these patients. General developmental disorder with retarded neurocognitive and motor function is present in all three patients.

Discussion

The use of extracorporeal membrane oxygenation in the treatment of newborns with CDH was introduced in the late 1970s. German., *et al.* reported on four infants who were placed on ECMO for severe respiratory failure after surgical CDH-repair with one of them surviving [21]. In 1996, the UK Collaborative ECMO Trial Group published their results of a randomized, controlled trial comparing outcomes of newborns with severe respiratory failure treated with ECMO or with conventional management only [22]. They included 185 patients; only 35 patients (19%) of the enrolled patients had CDH as underlying disease. They could show a significant difference in mortality in favor of ECMO-treated patients (32% vs. 59%). Consequently, ECMO became a standard treatment option for neonates who could not be managed with maximal conventional therapy and was supposed to improve survival rates of these patients [22]. Since then, the management of those patients has changed substantially. Along with the improvement of conventional respiratory management including gentle ventilation and implementation of new ventilation strategies such as HFOV and pharmacological treatment options such as inhalative NO an improved outcome of newborns with CDH could be noted in the last decades. In addition, current treatments strategies delayed surgery in order to optimize those patients prior to surgical therapy [15,23]. ECMO may provide short term support in case of respiratory failure. Therefore, one of the main requirements for indicating ECMO is the reversibility of the underlying disease. In CDH patients respiratory failure results from pulmonary hypoplasia and/or pulmonary hypertension, respectively. Pulmonary hypertension is potentially reversible, whereas depending on its degree pulmonary hypoplasia could be possibly irreversible. A careful patient selection is crucial in order to define those who could possibly benefit from ECMO. Until now neither clearly defined criteria for ECMO use nor standardized exclusion criteria exist. As management strategies for CDH as well as disease severity vary strongly, interpretation of outcomes in different centers and thus the proof of efficacy of ECMO is difficult [13,17-19,24]. Another important aspect when discussing dispensability of ECMO is the morbidity that is caused by ECMO itself. Long-term sequelae of ECMO treatment in early childhood are often underestimated. Application of ECMO is associated with significant pulmonary, gastrointestinal and neurologic morbidity especially in patients with CDH [25-30].

Reviewing the present literature, the benefit of ECMO in neonates with CDH remains unclear. Several studies suggest an improved survival with ECMO, however, randomised studies and meta-analyses could not prove a benefit of ECMO in terms of survival rates yet [17,24,31]. A Cochrane Review of 2008 comparing ECMO with conventional ventilatory support in neonates concluded that the benefit of ECMO is still unclear for CDH-patients [31].

In 2006 Morini., *et al.* published a systematic review of the evidence of ECMO in newborns with CDH [17]. They reviewed 21 non-randomised studies including 2043 patients and compared mortality between periods with ECMO being available and ECMO being not available. A high variability in inclusion and exclusion criteria for ECMO treatment between centers was described. They found a reduction in mortality in favor of ECMO-treated patients but questioned strongly the effect of improvement of conventional treatment modalities on mortality reduction as reported studies covered a time span of more than 40 years. In addition, they analysed three randomised, controlled trials (RCTs), including 39 patients and comparing ECMO with conventional ventilation. In summary they concluded that no long-term benefit for children treated with ECMO could be proven [17]. Another systematic review was performed by Logan., *et al* [24]. They included 13 reports from 11 centers containing 763 CDH-patients with an overall survival of 79% and 85% survival rate for isolated CDH. 40% of newborns with isolated CDH were placed on ECMO with a survival rate of 73%. Survival of patients managed without ECMO was 90%. The authors criticized the high variability of ECMO-indications and outcomes between centers as well as they questioned the impact of improvement of respiratory and pharmacological treatment modalities on increasing survival rates [24].

Multiple retrospective studies assessing survival of CDH patients treated with or without ECMO were carried out in the last decades. Schaible., *et al.* published the results of 321 neonates treated with ECMO in their referral center from 1987 - 2006, survival rate of

neonates with CDH was 62% [32]. Davis., *et al.* evaluated the outcome of all newborns with CDH in the United Kingdom (UK) who were treated with ECMO from 1991 - 2000 in a retrospective review (n = 73) [30]. They report a low survival rate with 27 patients surviving up to 1 year of age (37%) and high morbidity among these patients with only 7 children being free from any physical problems during long-term follow up [30]. In 2014 Zalla., *et al.* published their results of all liveborn CDH patients (n = 193) treated in their institution in Utah, USA from 1998 - 2003 [23]. They identified a reduction of mortality over time in their post-hoc analysis suggesting a relation to introduction of ECMO. They questioned if increased survival rates can be attributed to ECMO only or if also more effective management of pulmonary hypertension had an impact on these outcomes [23].

Comparing our results to those data, survival rates of our patients treated without ECMO proved to be not inferior to those reported by ECMO-centers. The survival rate of all newborns with CDH admitted in our institution including those newborns with major comorbidities was 83%. Survival of patients with isolated CDH was 92%. This is comparable if not even superior to data published by Logan., *et al.* [24] (overall survival: 79%, survival isolated CDH 85%). Survival of our neonates, who did fulfil ECMO-criteria but were treated with conventional management only was 75% whereas survival rates of patients treated with ECMO in literature remain much lower. Schaible., *et al.* reported on a survival rate of 62% [32] and in the United Kingdom only 37% of the patient cohort survived after ECMO treatment [30]. In addition, more than 90% of these infants suffered from relevant long-term morbidity [30]. In our cohort, there were only 3 patients suffering from major long-term sequelae which amounts to 38% among the potential ECMO-candidates and 12% of all CDH-patients.

Conclusions

In conclusion our study supports the thesis that ECMO might be dispensable for a majority of patients with CDH. As data in literature could not proof a benefit of ECMO in this patient population so far, a more critical appraisal for the indication of ECMO in patients with CDH is recommended. Along with the ongoing improvement of conventional respiratory therapy in these patients, the need to define criteria and subsequent common guidelines for the indication and application of ECMO is obvious. This seems to be more urgent as a rather liberal use of ECMO with its consecutive complications and longterm sequelae remains significant and impairs the lives of affected children.

Authors are aware of the limitations in the presented study. One limitation is the retrospective study design with admitting the possibility for missing data and unexpected confounders. In addition, the main limitation of the study is the small number of patients treated in our institution during the observation period.

Conflict of Interest

The authors declare that there is no financial interest or any conflict of interest.

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