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The role of extracorporeal life support and timing of repair in infants with congenital diaphragmatic hernia

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ABSTRACT

Extracorporeal life support (ECLS) serves as a rescue therapy for patients with congenital diaphragmatic hernia (CDH) and severe cardiopulmonary failure, and only half of these patients survive to discharge. This costly intervention has a significant complication risk and is reserved for patients with the most severe disease physiology refractory to maximal cardiopulmonary support. Some contraindications to ECLS do exist such as coagulopathy, lethal chromosomal or congenital anomaly, very preterm birth, or very low birth weight, but many of these limits are being evaluated through further research. Consensus guidelines from the past decade vary in recommendations for ECLS use in patients with CDH but this therapy appears to have a survival benefit in the most severe subset of patients. Improved outcomes have been observed for patients treated at high-volume centers. This review details the evolving literature surrounding management paradigms for timing of CDH repair for patients receiving preoperative ECLS. Most recent data support early repair following cannulation to avoid non-repair which is uniformly fatal in this population. Longer ECLS runs are associated with decreased survival, and patient physiology should guide ECLS weaning and eventual decannulation rather than limiting patients to arbitrary run lengths. Standardization of care across centers is a major focus to limit unnecessary costs and improve short-term and long-term outcomes for these complex patients.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is associated with an array of cardiopulmonary developmental sequelae including pulmonary hypoplasia with impaired gas exchange, pulmonary hypertension, and cardiac dysfunction. CDH is the most common respiratory indication for extracorporeal life support (ECLS, also known as extracorporeal membrane oxygenation or ECMO) for pediatric patients in the USA.[1] For those patients with respiratory failure and pulmonary insufficiency due to severe CDH, ECLS serves as a rescue intervention or bridging therapy to allow opportunity for surgical repair and improvement in cardiopulmonary function.

Unfortunately, CDH survivors have significant adverse outcomes that persist into adulthood despite survival to discharge, with greater severity of limitations in patients who undergo ECLS.[2 3] Ongoing research is aimed at optimizing patient selection for and techniques of ECLS in order to improve both survival and long-term outcomes for these populations with high-risk CDH. Given that treatment of patients with ECLS is costly with a marked complication rate and that notable significant disparities in patient mortality exist between centers, ECLS is a major target for standardization of care.[4 5] In this review, we will discuss existing international guidelines and consensus agreements on the use of ECLS for patients with CDH and highlight the literature and controversies that still exist regarding the temporal relationships between ECLS and CDH repair.

Predicting disease severity and use of ECLS

While overall survival for children with CDH has been increasing over the past three decades, mortality rates for patients who receive ECLS have remained stable at around 50%.[6] Several antenatal and postnatal risk stratification tools have been developed and validated to anticipate severe disease physiology and therefore guide prenatal counseling, expedite referral or transfer to specialized centers with ECLS capabilities, and establish goals and limits of care.

Four well-established risk stratification metrics obtained from prenatal imaging include observed-to-expected lung-to-head ratio (O/E LHR) via ultrasound and observed-to-expected total fetal lung volume (O/E TFLV), percent predictive lung volume (PPLV), and percent liver herniation via fetal MRI (thoracic liver position or "liver-up" is a poor prognostic factor in left-sided CDH).[7] Ultrasound-obtained O/E LHR of <25% is predictive of a <50% chance of survival, whereas >40% is predictive of >80% survival.[8–10] Cut-off values ranging from 25% to 35% O/E TFLV have been most frequently cited, with lower values predictive

of mortality, ECLS use, and other outcomes of pulmonary morbidity such as bronchopulmonary dysplasia (BPD) when compared with patients with higher calculation.[11–13] One multicenter study of 77 prospectively assessed patients found a 19% chance of survival with O/E TFLV <25% compared with 40.3% in the >25% O/E TFLV group (p=0.008).[14] The derivation publication for PPLV evaluating 14 patients found that PPLV <15% was associated with significantly lower survival (40%, 2/5), ECLS use (100%, 5/5), and longer hospital length of stay compared with 100% (9/9) survival and 11% (1/9) ECLS use.[14] A later validation study evaluating MRI-based predictors for 80 fetuses used <10.2 and <10.3 as cutoffs for predictors of mortality and ECLS use, respectively, with a C-statistic of 0.74 for both.[11] The most frequent threshold used for percent liver herniation is >20%, yielding C-statistics reported between 0.74 and 0.78 for prediction of both ECLS use and mortality, with mortality estimated at 36%[12] and odds ratios (ORs) for mortality and ECLS use estimated at 7.4 and 8.6, respectively.[11–13 15]

Several validated postnatal risk prediction tools combine clinical risk factors from the first 24 hours of life to provide estimates of survival or mortality. These factors include birth weight, Apgar Scores at 1 and 5 min, FiO_2 requirement, blood gas measurements such as pH, PaO_2, and $PaCO_2$, and concomitant conditions such as pulmonary hypertension, cardiac or chromosomal anomaly, or presence of seizures.[12 16–20] Diaphragmatic hernia size strongly correlates with mortality risk, but this measurement can only be obtained during operative repair and thus is useful for standardizing reporting for multicenter registries and retrospective analyses but cannot be used for preoperative prediction or clinical decision-making.[21] The CDH Study Group (CDHSG) created a simple validated survival prediction tool using a combination of 5-minute Apgar Score and birth weight.[16] Preterm birth has also been identified as a risk factor for mortality but has not been incorporated into any widely used risk prediction models as of yet.[22] A modified model was published by Brindle *et al.* in 2014 and later validated which classified infants into low (~10%), intermediate (~20%), or high (~50%) risk of death using the factors very low birth weight, absent/low 5-minute Apgar Score, chromosomal or major cardiac anomaly, and suprasystemic pulmonary hypertension.[18 20] A recent review by Jancelewicz and Brindle on these prediction tools proposed a prognostic schema for practitioner use to incorporate prenatal imaging at 22 and 30 weeks gestational age as well as established risk calculators, echocardiogram and serial blood gas measurements postnatally.[23]

Unsurprisingly, the same prenatal imaging and postnatal clinical factors used in disease severity and mortality risk prediction models also predict ECLS utilization probability.[23–26] Early postnatal blood gas measurements serve as particularly useful and dynamic indicators of functional gas exchange to predict ECLS use. An ECLS risk stratification model was developed using CDHSG data to predict a composite outcome of ECLS use or death without ECLS; the four final variables included in the model were Apgar Scores at 1 and 5 min and highest and lowest postductal $PaCO_2$ measurements during the first day of life.[24] Broadly, prenatal predictive tools and postnatal disease severity indicators or predictive models can provide an individualized risk profile for death or ECLS requirement that is likely to be more accurate than any solitary risk estimation tool alone.[11 23] Early and repeated calculated risk estimates can assist providers in deciding if and when to initiate ECLS. Risk stratification is vital to identify those patients most likely to benefit from ECLS, which will enable an earlier transition to ECLS, avoid ongoing lung injury in vain attempts to delay its use, and prevent the need for emergent cannulation.

Indications for ECLS and patient selection

ECLS is reserved for the most severe cases of patients with CDH who are actively or expected to clinically deteriorate from a cardiopulmonary standpoint despite maximal ventilatory and hemodynamic support. Postnatal intensive care ventilation principles include limiting barotrauma and volutrauma with permissive hypercapnia.[27] Both conventional and high-frequency oscillatory ventilation modes are used and multiple recent retrospective multicenter trials have demonstrated no differences in primary outcomes of death, BPD, or length of oxygen support,[28–30] but one multicenter randomized trial (the "VICI" trial) demonstrated improved secondary outcomes of total mechanical ventilation time and ECLS avoidance with conventional mode.[31] Management of pulmonary hypertension with sildenafil, milrinone, or prostacyclin analogs is frequently done despite the fact that much of the evidence for their use is imparted from adult data and non-CDH pediatric pulmonary hypertension etiologies.[32 33] Inhaled nitric oxide is a frequently used adjunct for management of pulmonary hypertension during the initial resuscitation period, but its clinical benefit has not been definitively demonstrated prospectively and may be associated with increased mortality or use of ECLS.[34–36] Secondary right-sided cardiac dysfunction is managed by reducing pulmonary hypertension with the above strategies and maintaining patent ductus arteriosus patency. Early left ventricular dysfunction is a poor prognostic factor in patients with CDH[37]; therapy is aimed at afterload reduction, preload optimization, and judicious use of inotropic agents.

While pulmonary hypoplasia is not a reversible pathology in the short term, the rationale for early ECLS cannulation for patients who meet threshold criteria indications is to reduce further ventilator-associated lung injury, pulmonary hypertension exacerbation, and sequelae of persistent hypoxia and acidosis.[38 39] Generally accepted indications for ECLS initiation include persistently inadequate oxygen delivery with metabolic acidosis, persistent hypoxia or significantly elevated mechanical ventilation settings to maintain oxygenation, hypercarbia, pulmonary hypertension, and/or cardiac dysfunction, and systemic hypotension refractory to fluid

and inotropic support.[5 31 40 41] After the decision is made for ECLS initiation, the principles of lung-protective ventilation and mitigating pulmonary hypertension and cardiac dysfunction continue to apply.

According to the Extracorporeal Life Support Organization (ELSO) guidelines for ECLS use in children with respiratory failure, absolute contraindications for ECLS are significant intraventricular hemorrhage or other uncontrolled hemorrhage (in other words, contraindications to anticoagulation), severe brain damage, lethal chromosomal anomaly or other lethal malformation, and inadequate vessel caliber for cannulation.[40] Relative contraindications according to this group are end-stage organ dysfunction unless being considered for transplant, preterm birth <34 weeks gestational age, and birth weight <2 kg.[40]

As indications for ECLS have grown in the past several years and with intercenter practice variability accounting for some newborns with significant comorbidities receiving ECLS, these contraindications are being refined.[42–45] Some experts have found that even among infants with the highest physiologic severity measures, survival can still be upwards of 50% if patients are treated for survival and that no infants should be considered "too sick" to undergo ECLS.[43] Church *et al.* analyzed ELSO registry data and found similar survival between patients with CDH born at 29–33 weeks gestational age when compared with 34 weeks gestational age.[44] Other groups have found that CDH with concomitant major congenital cardiac diseases such as hypoplastic left heart syndrome and single ventricle physiology who undergo ECLS have more favorable outcomes than expected.[45–47] There is therefore some evidence that major cardiac malformations may be viewed as relative rather than absolute contraindication to ECLS in patients with CDH.

Mortality benefits and impact of center volume/experience

Paradoxically, overall survival rates for children with CDH who receive ECLS have actually declined in recent years despite improved safety, which is thought to be due to a greater number of patients with severe CDH surviving to be eligible for ECLS.[6 48 49] Earlier studies had mixed conclusions regarding the benefit of ECLS in CDH; multiple cohort studies found no survival benefit and others were more optimistic.[27 50–53] However, more recent data have demonstrated a survival benefit for patients with severe CDH and those cared for at experienced centers.[54] In one of the few randomized controlled trials comparing ECLS to conventional therapy in neonates with severe respiratory failure, the UK Collaborative ECMO Trial Group found among patients with CDH as a primary diagnosis, 14 of 18 (77.8%) allocated to ECLS died while all 17 (100%) allocated conventional ventilation died.[55] A 2006 systematic review and meta-analysis of 21 non-randomized studies (total of 2043 patients) found relative risks of death before discharge of 0.60 (95% confidence interval (CI) 0.51 to 0.70; $p<0.001$) and late or postdischarge death of 0.63 (95% CI 0.53 to 0.73; $p<0.001$) when ECLS was available.[56] Perhaps most convincingly, a retrospective propensity-matched analysis of 5855 ECLS-eligible patients from the CDHSG registry identified a survival benefit with ECLS in patients with high-risk CDH, with mortality of 64.2% in the ECLS group versus 84.4% in the non-ECLS group (OR 0.33, 95% CI 0.17 to 0.65; $p=0.001$).[57] This survival benefit, notably, was found predominantly at high-volume centers (≥10 cases of CDH per year).[57] The effect of improved survival at high-volume centers for both all patients with CDH and patients with CDH undergoing ECLS has been corroborated in studies of other databases such as the Kids' Inpatient Database, Pediatric Health Information Systems, and the ELSO registry even after risk adjustment.[58–60] However, high-volume centers with ≥10 patients with CDH annually appear to be less cost-effective overall than low-volume centers.[61 62] This variation in outcomes and cost points to a clear need for standardization of care across centers.

In conclusion, these recent data demonstrate that while most patients with CDH do not benefit from ECLS, those with the most severe disease phenotypes appear to have a small but significant survival benefit, and center experience and volume play a major role in the success of this therapy.[63]

Consensus guidelines

The European CDH Consortium (2016) and Canadian CDH Collaborative (2018, revised in 2023) clinical practice guidelines hold conservative recommendations for ECLS use.[64 65] The European group's consensus provided relative indications for ECLS initiation and a low-grade recommendation that CDH can be repaired while the patient is on ECLS, citing conflicting results of retrospective studies comparing timing of CDH repair in regards to ECLS.[64] In 2018, the Canadian group, which used a rigorous grading methodology to derive recommendations, recommended prenatal counseling for families of children with prenatally diagnosed CDH of the possibility of ECLS use, stating "current evidence does not suggest a survival benefit," with a concession that when ECLS is considered as a rescue therapy that standard contraindications should apply.[65] The 2023 update to the Canadian consensus modified the latter recommendation, although with weak agreement, that ECLS may be offered to patients in certain circumstances and with size, age, and comorbidity contraindications.[66] The American guidelines do not specifically provide any recommendations about the use of ECLS in patients with CDH but write that they assume ECLS provides a survival benefit; they do conclude that there appears to be no survival benefit based on mode of ECLS (venovenous or venoarterial) but that venovenous mode may be preferred due to a lower complication risk.[67] Further discussion on the preferred mode of ECLS is outside of the scope of this review. However, the most comprehensive consensus guidelines for ECLS use in CDH come from the previously mentioned ELSO 2021 publication by Guner *et*

al.[5] This organization is an international consortium of providers and institutions chiefly concerned with research and education on ECLS broadly. Apart from discussing indications and contraindications for ECLS in patients with CDH, this publication further provides recommendations on risk stratification for ECLS, early postnatal care and pulmonary hypertension management, and technical aspects of ECLS such as pump type, mode of support, and cannulation. These ELSO guidelines and the most recent edition of the Canadian guidelines also provide recommendations for timing of CDH repair as well as length of ECLS runs, which are discussed below. A summary of pertinent recommendations provided by these organizations is provided in table 1.

Timing of CDH repair and its relation to ECLS

The timing of CDH repair in relation to ECLS continues to be controversial. Timing of repair can be classified as pre-ECLS, early on-ECLS, delayed on-ECLS, or post-ECLS decannulation. Variations in preferred approaches for those who arrive to ECLS prior to repair continue to exist between centers. In this section, we will discuss the changes of management dogma over time.

For many years, CDH was considered a surgical emergency, and immediate repair was thought to be the best to decompress the thoracic cavity. In the 1990s with the broadening adoption of ECLS for patients with severe CDH, the pendulum began to swing in the opposite direction with multiple studies associating improved outcomes with achieving preoperative hemodynamic stability with or without ECLS treatment followed by delayed, semielective repair off ECLS (if used) to allow for lung recovery and potential pulmonary hypertension improvement.[68–71] Still, some centers had contrary results, and a 2000 Cochrane systematic analysis concluded that there existed no clear evidence for delayed (>24 hours) surgical intervention after stabilization over early (<24 hours) repair, owed to heterogeneity of trials and limited prospective data at that time.[72 73] In a study of 1385 CDHSG registry patients who underwent operative repair without preoperative ECLS, crude analysis showed significantly greater mortality among those undergoing repair between days of life (DOL) 4–7 (6.6%) and DOL ≥8 (12.3%), compared with DOL 0–3 (3.9%).[74] However, in this study delayed repair was associated with increased CDH and comorbidity severity, suggesting that physiologic stabilization prior to repair takes a longer time in this group and after adjusting for these factors the survival effect was no longer significant.[74] In a single high-volume institution study, 60/87 ECLS-eligible infants with left "liver up" (a high-risk phenotype) CDH received ECLS, and early repair within 60 hours of birth for those with an appropriate "window" for repair prior to ECLS was associated with improved survival over those who arrived to ECLS unrepaired (21/22, 95% vs 13/20, 65%; p=0.0018).[8] Notably, this comparison did not include infants who received ECLS within 12 hours of life. Nevertheless, the blanket approach of delayed repair was promulgated for some time including patients who did undergo preoperative ECLS. Further supporting the delayed after-ECLS repair approach, a 2009 study of CDHSG registry data on 636 patients over a span of 10 years who underwent repair and ECLS therapy compared outcomes of on-ECLS and off-ECLS repair; this group found a significant survival benefit to repair after ECLS relative to repair on ECLS with a hazard ratio of 1.41.[75] Other single-center retrospective studies performed in the USA demonstrated similar results.[76 77] A later analysis of a larger cohort of 2244 infants from the ELSO registry who underwent ECLS and surgical repair also found improved survival in those able to be weaned and decannulated from ECLS prior to repair when compared with on-ECLS repair, even after propensity score matching for disease severity and mortality risk.[78] This analysis also noted increased run lengths of ECLS and higher risks of significant neurological injury in the on-ECLS group.

More recent data from the 2010s and later have led to another paradigm shift in the management of repair timing for patients with severe CDH, favoring earlier repair for those who arrive to ECLS unrepaired. The previously discussed on-versus-after ECLS analyses have been limited by selection bias from excluding children who did not undergo repair such as those who experienced fatal complications of ECLS (i.e., hemorrhage or significant neurological injury) or those who were otherwise too critically ill to undergo surgery. In other words, patients who died prior to repair and were excluded from these studies may have benefited from earlier, protocolized repair on ECLS, and their exclusion may introduce bias into studies comparing on-ECLS to post-ECLS repair (to favor post-ECLS repair). Moreover, these studies are confounded by not accounting for timing of on-ECLS repair and by including patients who undergo late or salvage repair who had not yet reached the critical milestone of weaning off ECLS and recovery.[63 75] As such, potential clinical benefit from early-on-ECLS CDH repair compared with post-ECLS may be diluted in existing studies by grouping these early-ECLS patients together with patients who undergo repair late in their ECLS runs due to failure to wean, which is associated with increased morbidity and mortality.[79] Initial support for early repair on ECLS came from a single-center study that compared their institutional protocol (repair 24–72 hours after cannulation) to the CDHSG data (average repair at approximately 7 days after cannulation) and ELSO data.[80] Within their institution, 100% (34/34) of neonates on ECLS were repaired according to their protocol and analysis showed an increase in survival (71% vs 50.9%), as well as a comparable complication profile, relative to late on-ECLS repair in the CDHSG data set.[80] Another single institution evaluated the effect of protocolizing repair timing into three groups: within 72 hours after ECLS cannulation, >72-hour post-cannulation, and post-decannulation. The authors found greatest survival in the early repair group (73% vs 50% vs 64%, respectively) and decreased ECLS complications when compared with

Table 1 Summary of existing national consensus guidelines on use of ECLS in patients with CDH

Organization	Origin	Date of publication	Key CDH-ECLS recommendations	Strength of agreement or recommendation	Level of evidence
American Pediatric Surgery Association	USA	2015	Assumed survival benefit of ECLS in patients with CDH	N/A	N/A
			No survival advantage for VA versus VV mode ECLS	Grade C (A to D)	Class 3–4 (case–control studies, case series)
			Arbitrary ECLS run lengths should be avoided; up to 4 weeks with acceptable survival	Grade D (A to D)	Class 4 (case series, expert opinion)
Canadian CDH Collaborative	Canada	2023	ECLS indications: respiratory or circulatory failure or acute clinical deterioration (agreement with ELSO)	N/A	N/A
			Prenatal counseling for families of patients with prenatal CDH diagnosis regarding possibility of ECLS	Good agreement (3 out of 4)	Level B (non-randomized data)
			Timing of repair: CDH repair should be avoided until after ECLS decannulation; palliation versus surgery for those unable to wean off ECLS	Good agreement (3 out of 4)	Level B (non-randomized data)
			Contraindications: ECLS may be considered in populations with size/age or comorbidity contraindications under special circumstances (experimental scenarios or high-volume centers)	Weak agreement (2 out of 4)	Level C (limited data)
			Timing of repair: Patients with low probability of survival based on prenatal predictors or severity of cardiopulmonary derangement at cannulation may benefit from early repair	Good agreement (3 out of 4)	Level B (non-randomized data)
Euro CDH Consortium	Multinational	2015	ECLS indications: based on values for oxygenation, blood gas, and ventilatory parameters, refractory hypotension, or decreased urine output	Grade D (A to D)	Not provided
			Timing of repair: CDH repair should be attempted after clinical stabilization, with definitions based on blood pressure, preductal SpO_2, FiO_2, serum lactate, and urine output	Grade D (A to D)	Not provided

Continued

Table 1 Continued

Organization	Origin	Date of publication	Key CDH-ECLS recommendations	Strength of agreement or recommendation	Level of evidence
Extracorporeal Life Support Organization (ELSO)	Multinational	2021	ECLS indications: hypoxic or hypercapnic respiratory failure, circulatory failure, or acute clinical deterioration	N/A	N/A
			Contraindications: gestational age <32 weeks, birth weight <1.7–2.0 kg, major genetic abnormalities/syndromes (relative). Severe congenital cardiac disease also a contraindication, but case-by-case discussion is needed.		
			Timing of repair: patients who can be decannulated or weaned off ECLS may benefit from delaying repair until decannulation, but risk of delayed salvage repair on ECLS exists; patients with severe phenotype may benefit from early repair on ECLS		
			Other topical recommendations provided: risk stratification, early postnatal care, management of pulmonary hypertension, mode of support, cannulation, pump time, on-ECLS ventilation strategies		

CDH, congenital diaphragmatic hernia; ECLS, extracorporeal life support; ELSO, extracorporeal life support organization; VA, veno-arterial; VV, veno-venous.

the late on-ECLS group.[81] The 2015 American guidelines based on a systematic review could not recommend a one-size-fits-all generalized approach for the timing of CDH repair given the heterogeneity of disease severity but concluded based on these two studies in addition to previous papers that "early repair on ECLS may have improved survival and shorter ECLS duration" with a grade D recommendation.[67]

The limitations of the on-versus-after ECLS repair studies were largely overcome in a propensity-matched study from the CDHSG registry by Dao *et al.* wherein outcomes of early and late on-ECLS versus late after-ECLS repair were evaluated.[82] By accounting for the risk of non-repair, these data showed convincingly a significant decrease in mortality of early on-ECLS repair (median time to repair: 2 days) compared with late on-ECLS (median time to repair: 12 days) or late after-ECLS repair. Moreover, the early group in this study had significantly decreased length of stay versus late repair (median 54 vs 95 days) and trends toward lower supplemental oxygen requirement and higher oral feeding at discharge, but these differences were not significant.[82] Notably, once non-repairs were excluded, the survival benefit associated with early repair was reversed, similar to the 2019 study by Delaplain *et al.* using data from the ELSO registry to compare on-ECLS versus after-ECLS outcomes.[78] Further support for early repair comes from another large study using the CDHSG data set comparing early on-ECLS repair with delayed after-ECLS repair, showing increased odds of survival to hospital discharge despite longer ECLS runs and increased risk factors such as intrathoracic liver and cardiac defects.[83] In contrast to the American guidelines, the Canadian consensus guidelines hold a general recommendation to defer CDH repair until decannulation from ECLS, but patients at highest mortality risk based on preoperative factors such as prenatal predictors or cardiopulmonary instability at cannulation may benefit from early on-ECLS repair.[65] Key papers comparing outcomes along the ECLS timeline are represented in figure 1.

We conclude that for patients who arrive to ECLS prior to repair, early repair on ECLS is probably the optimal protocol despite potential for increased ECLS run lengths and neurologic injury; this approach avoids non-repair which is uniformly fatal in patients on ECLS, restores normal thoracic anatomy to facilitate subsequent

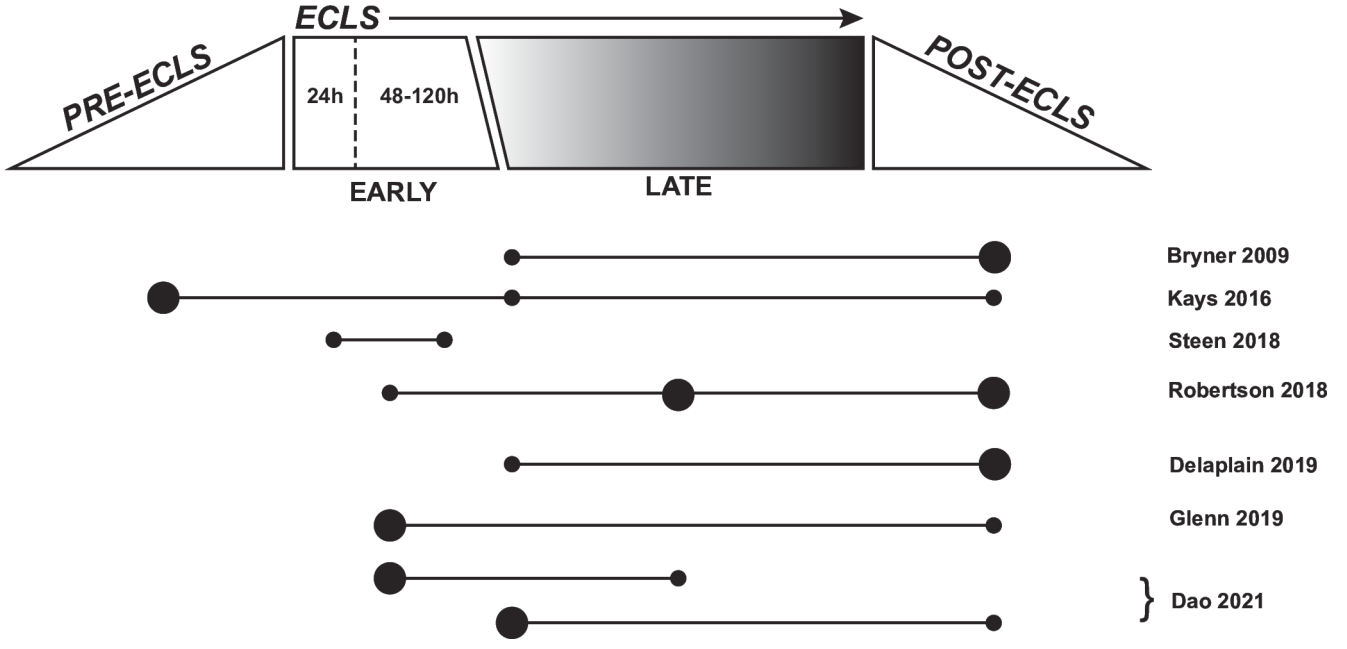

Figure 1 Key manuscripts regarding timing of surgical repair for infants with CDH receiving ECLS. Lines indicate group comparisons in the manuscript, with larger dots denoting improved outcomes over smaller dots in the respective group. Summaries of findings are as follows. Bryner *et al.*[75] and CDHSG 2009; improved survival in post-ECLS versus on-ECLS group (excluded non-repairs). Kays *et al.*[8]; among high-risk left liver-up infants that received ECLS, improved survival with <60-hour of life repair pre-ECLS versus composite on-ECLS or post-ECLS repair (excluded infants receiving ECLS within 12 hours of life). Steen *et al.*[86]; <24 hours versus 24–72 hours early repair associated with no increased mortality, hospital stay, ventilator days, or ECLS run lengths. Robertson *et al.*[77]; early <5 days repair versus composite late-ECLS or after-ECLS repair associated with increased mortality, ECLS run length. Delaplain *et al.*[78] and ELSO 2019; propensity-matched on-ECLS versus post-ECLS; increased mortality and neurological injury in on-ECLS group (excluded non-repairs). Glenn *et al.*[83] and CDHSG 2019; increased survival odds, longer ECLS run lengths, increased intrathoracic liver and cardiac defects associated with <72-hour early repair versus post-ECLS repair. Dao *et al.*[82] and CDHSG 2021; propensity-matched on-ECLS versus post-ECLS and early-ECLS versus late-ECLS comparisons; lower mortality and non-repair rates in on-ECLS and early-ECLS approach. Shorter hospital stay, ECLS run length in early group. CDH, congenital diaphragmatic hernia; CDHSG, CDH Study Group; ECLS, extracorporeal life support.

weaning from ECLS, simplifies the operation before edema and other ECLS complications occur, and likely reduces bleeding complications.[84–87]

Length of ECLS

Currently, there are no firm recommendations on a maximum length or limit on ECLS support, but there is a clear association between longer ECLS runs and increased mortality and complications such as circuit issues, hemorrhage, sepsis, fluid overload, renal insufficiency, and neurological injury.[79]

The degree of pre-ECLS support and complications certainly impact the length of ECLS and the development of multiorgan failure while on ECLS.[88] The timing of weaning from ECLS and eventual decannulation are based on patient physiology and center-specific factors. In a single center study in the UK, ECLS runs longer than 2 weeks carried a significantly higher mortality rate than those less than 2 weeks (18% vs 68%).[89] A retrospective single-center study demonstrated decreasing survival for patients with CDH requiring ECLS after 2 weeks, with 56% at 3 weeks, 46% at 4 weeks, <15% after 5 weeks, and no survival at or after 40 days.[90] In this study, a prolonged ECLS run was associated with multiple markers of severity. These authors concluded that stabilization of patients on ECLS may take over 4 weeks and that arbitrary run lengths shorter than this time should be avoided in order to limit overaggressive ECLS weaning which could lead to repeat ECLS runs.[90] Additional studies demonstrated that comorbid conditions, low birth weight, and use of inotropes, which may indicate higher risk in general, did not predict longer ECLS runs.[87] Repeat ECLS runs are also associated with increasing morbidity and mortality but it has been postulated that offering repeat ECLS runs may have potential to improve overall survival.[91]

CONCLUSION

The recommendations for ECLS use in CDH vary and practice patterns have changed significantly in recent decades. ECLS is an effective rescue and bridging therapy to surgical repair for a small subset of patients with severe CDH and is best avoided in low-risk and moderate-risk patients. High center volume and experience have been shown to improve outcomes for patients with CDH who undergo ECLS. Finding the optimal timing of surgical repair for patients with CDH across the disease severity spectrum, particularly those who receive preoperative ECLS, has been a major challenge and a topic of significant debate due to the lack of high-quality prospective data. For patients who are treated with preoperative ECLS, contemporary literature suggests that early repair while on ECLS is preferable to delayed on-ECLS or post-ECLS repair. In weaning patients from ECLS, arbitrary run lengths are best avoided.

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REFERENCES

1 Qureshi FG, Jackson HT, Brown J, *et al*. The changing population of the United States and use of extracorporeal membrane oxygenation. *J Surg Res* 2013;184:572–6.
2 Spoel M, van der Cammen-van Zijp MHM, Hop WCJ, *et al*. Lung function in young adults with congenital diaphragmatic hernia; a longitudinal evaluation. *Pediatr Pulmonol* 2013;48:130–7.
3 Kraemer US, Kamphuis LS, Ciet P, *et al*. Cardiopulmonary morbidity in adults born with congenital diaphragmatic hernia. *Pediatrics* 2023;152:e2023062341.
4 Guner YS, Harting MT, Jancelewicz T, *et al*. Variation across centers in standardized mortality ratios for congenital diaphragmatic hernia receiving extracorporeal life support. *J Pediatr Surg* 2022;57:606–13.
5 Guner Y, Jancelewicz T, Di Nardo M, *et al*. Management of congenital diaphragmatic hernia treated with extracorporeal life support: interim guidelines consensus statement from the extracorporeal life support organization. *ASAIO J* 2021;67:113–20.
6 Guner YS, Delaplain PT, Zhang L, *et al*. Trends in mortality and risk characteristics of congenital diaphragmatic hernia treated with Extracorporeal membrane oxygenation. *ASAIO J* 2019;65:509–15.
7 Mullassery D, Ba'ath ME, Jesudason EC, *et al*. Value of liver herniation in prediction of outcome in fetal congenital diaphragmatic hernia: a systematic review and meta-analysis. *Ultrasound in Obstet &Amp; Gyne* 2010;35:609–14.
8 Kays DW, Talbert JL, Islam S, *et al*. Improved survival in left liver-up congenital diaphragmatic hernia by early repair before extracorporeal membrane oxygenation: optimization of patient selection by multivariate risk modeling. *J Am Coll Surg* 2016;222:459–70.
9 Snoek KG, Peters NCJ, van Rosmalen J, *et al*. The validity of the observed-to-expected lung-to-head ratio in congenital diaphragmatic hernia in an era of standardized neonatal treatment; a multicenter study. *Prenat Diagn* 2017;37:658–65.
10 Jani J, Nicolaides KH, Keller RL, *et al*. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2007;30:67–71.
11 Ruano R, Lazar DA, Cass DL, *et al*. Fetal lung volume and quantification of liver herniation by magnetic resonance imaging in isolated congenital diaphragmatic hernia. *Ultrasound in Obstet & Gyne* 2014;43:662–9.
12 Akinkuotu AC, Cruz SM, Abbas PI, *et al*. Risk-stratification of severity for infants with CDH: prenatal versus postnatal predictors of outcome. *J Pediatr Surg* 2016;51:44–8.
13 Zamora IJ, Olutoye OO, Cass DL, *et al*. Prenatal MRI fetal lung volumes and percent liver herniation predict pulmonary morbidity in congenital diaphragmatic hernia (CDH). *J Pediatr Surg* 2014;49:688–93.
14 Gorincour G, Bouvenot J, Mourot MG, *et al*. Prenatal prognosis of congenital diaphragmatic hernia using magnetic resonance imaging measurement of fetal lung volume. *Ultrasound in Obstet & Gyne* 2005;26:738–44.

15 Lazar DA, Ruano R, Cass DL, *et al*. "Defining "liver-up": does the volume of liver herniation predict outcome for fetuses with isolated left-sided congenital diaphragmatic hernia" *J Pediatr Surg* 2012;47:1058–62.
16 Congenital Diaphragmatic Hernia Study Group. Estimating disease severity of congenital diaphragmatic hernia in the first 5 minutes of life. *J Pediatr Surg* 2001;36:141–5.
17 Schultz CM, DiGeronimo RJ, Yoder BA, *et al*. Congenital diaphragmatic hernia: a simplified postnatal predictor of outcome. *J Pediatr Surg* 2007;42:510–6.
18 Brindle ME, Cook EF, Tibboel D, *et al*. A clinical prediction rule for the severity of congenital diaphragmatic hernias in newborns. *Pediatrics* 2014;134:e413–9.
19 Skarsgard ED, MacNab YC, Qiu Z, *et al*. SNAP-II predicts mortality among infants with congenital diaphragmatic hernia. *J Perinatol* 2005;25:315–9.
20 Bent DP, Nelson J, Kent DM, *et al*. Population-based validation of a clinical prediction model for congenital diaphragmatic hernias. *J Pediatr* 2018;201:160–5.
21 Group CDHS, Lally KP, Lally PA, *et al*. Defect size determines survival in infants with congenital diaphragmatic hernia. *Pediatrics* 2007;120:e651–7.
22 Tsao K, Allison ND, Harting MT, *et al*. Congenital diaphragmatic hernia in the preterm infant. *Surgery* 2010;148:404–10.
23 Jancelewicz T, Brindle ME. Prediction tools in congenital diaphragmatic hernia. *Semin Perinatol* 2020;44:151165.
24 Jancelewicz T, Brindle ME, Harting MT, *et al*. Extracorporeal membrane oxygenation (ECMO) risk stratification in newborns with congenital diaphragmatic hernia (CDH). *J Pediatr Surg* 2018;53:1890–5.
25 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.
26 Hedrick HL, Danzer E, Merchant AM, *et al*. Liver position and lung-to-head ratio for prediction of Extracorporeal membrane oxygenation and survival in isolated left congenital diaphragmatic hernia. *Am J Obstet Gynecol* 2007;197:422.
27 Kays DW, Langham MR, Ledbetter DJ, *et al*. Detrimental effects of standard medical therapy in congenital diaphragmatic hernia. *Ann Surg* 1999;230:340–8; .
28 Semama C, Vu S, Kyheng M, *et al*. High-frequency oscillatory ventilation versus conventional ventilation in the respiratory management of term neonates with a congenital diaphragmatic hernia: a retrospective cohort study. *Eur J Pediatr* 2022;181:3899–906.
29 Fuyuki M, Usui N, Taguchi T, *et al*. Prognosis of conventional vs. high-frequency ventilation for congenital diaphragmatic hernia: a retrospective cohort study. *J Perinatol* 2021;41:814–23.
30 Morini F, Capolupo I, van Weteringen W, *et al*. Ventilation modalities in infants with congenital diaphragmatic hernia. *Semin Pediatr Surg* 2017;26:159–65.
31 Snoek KG, Capolupo I, van Rosmalen J, *et al*. Conventional mechanical ventilation versus high-frequency oscillatory ventilation for congenital diaphragmatic hernia: a randomized clinical trial (the VICI-trial). *Ann Surg* 2016;263:867–74.
32 Gupta VS, Harting MT. Congenital diaphragmatic hernia-associated pulmonary hypertension. *Semin Perinatol* 2020;44:151167.
33 Kipfmueller F, Schroeder L, Berg C, *et al*. Continuous intravenous sildenafil as an early treatment in neonates with congenital diaphragmatic hernia. *Pediatr Pulmonol* 2018;53:452–60.
34 Campbell BT, Herbst KW, Briden KE, *et al*. Inhaled nitric oxide use in neonates with congenital diaphragmatic hernia. *Pediatrics* 2014;134:e420–6.
35 Putnam LR, Tsao K, Morini F, *et al*. Evaluation of variability in inhaled nitric oxide use and pulmonary hypertension in patients with congenital diaphragmatic hernia. *JAMA Pediatr* 2016;170:1188–94.
36 Barrington KJ, Finer N, Pennaforte T, *et al*. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev* 2017;1:CD000399.
37 Patel N, Lally PA, Kipfmueller F, *et al*. Ventricular dysfunction is a critical determinant of mortality in congenital diaphragmatic hernia. *Am J Respir Crit Care Med* 2019;200:1522–30.
38 Rafat N, Schaible T. Extracorporeal membrane oxygenation in congenital diaphragmatic hernia. *Front Pediatr* 2019;7:336.
39 Wegele C, Schreiner Y, Perez Ortiz A, *et al*. Impact of time point of extracorporeal membrane oxygenation on mortality and morbidity in congenital diaphragmatic hernia: a single-center case series. *Children (Basel)* 2022;9:986.
40 Wild KT, Rintoul N, Kattan J, *et al*. Extracorporeal life support organization (ELSO): guidelines for neonatal respiratory failure. *ASAIO J* 2020;66:463–70.
41 Zani A, Chung WK, Deprest J, *et al*. Congenital diaphragmatic hernia. *Nat Rev Dis Primers* 2022;8.
42 Wong JJM, Cheifetz IM, Lee JH. n.d. Extracorporeal membrane oxygenation for severe pediatric respiratory failure. *J Emerg Crit Care Med*1:11.
43 Kays DW, Islam S, Perkins JM, *et al*. Outcomes in the physiologically most severe congenital diaphragmatic hernia (CDH) patients: whom should we treat. *J Pediatr Surg* 2015;50:893–7.
44 Church JT, Kim AC, Erickson KM, *et al*. Pushing the boundaries of ECLS: outcomes in <34 week EGA neonates. *J Pediatr Surg* 2017;52:1810–5.
45 Cairo SB, Arbuthnot M, Boomer LA, *et al*. Controversies in extracorporeal membrane oxygenation (ECMO) utilization and congenital diaphragmatic hernia (CDH) repair using a Delphi approach: from the American pediatric surgical association critical care committee (APSA-CCC). *Pediatr Surg Int* 2018;34:1163–9.
46 Dyamenahalli U, Morris M, Rycus P, *et al*. Short-term outcome of neonates with congenital heart disease and diaphragmatic hernia treated with extracorporeal membrane oxygenation. *Ann Thorac Surg* 2013;95:1373–6.
47 Ryan CA, Perreault T, Johnston-Hodgson A, *et al*. Extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia and cardiac malformations. *J Pediatr Surg* 1994;29:878–81.
48 Turek JW, Nellis JR, Sherwood BG, *et al*. Shifting risks and conflicting outcomes-ECMO for neonates with congenital diaphragmatic hernia in the modern era. *J Pediatr* 2017;190:163–8.
49 Saugstad OD. When increased mortality indicates improved care: CDH ECMO registry data. *J Pediatr* 2017;190:4–5.
50 Azarow K, Messineo A, Pearl R, *et al*. Congenital diaphragmatic hernia—a tale of two cities: the Toronto experience. *J Pediatr Surg* 1997;32:395–400.
51 Wilson JM, Lund DP, Lillehei CW, *et al*. Congenital diaphragmatic hernia--a tale of two cities: the Boston experience. *J Pediatr Surg* 1997;32:401–5.
52 Bartlett RH, Gazzaniga AB, Toomasian J, *et al*. Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure. 100 cases. *Ann Surg* 1986;204:236–45.
53 The Congenital Diaphragmatic Hernia Study Group. Does Extracorporeal membrane oxygenation improve survival in neonates with congenital diaphragmatic hernia? J Pediatr Surg 1999;34:720–5.
54 Schaible T, Hermle D, Loersch F, *et al*. A 20-year experience on neonatal extracorporeal membrane oxygenation in a referral center. *Intensive Care Med* 2010;36:1229–34.
55 UK collaborative randomised trial of neonatal Extracorporeal membrane oxygenation. UK collaborative ECMO trail group. *The Lancet* 1996;348:75–82.
56 Morini F, Goldman A, Pierro A. Extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia: a systematic review of the evidence. *Eur J Pediatr Surg* 2006;16:385–91.
57 Jancelewicz T, Langham MR Jr, Brindle ME, *et al*. Survival benefit associated with the use of extracorporeal life support for neonates with congenital diaphragmatic hernia. *Ann Surg* 2022;275:e256–63.
58 Martino AM, Nguyen DV, Delaplain PT, *et al*. Center volume and survival relationship for neonates with congenital diaphragmatic hernia treated with Extracorporeal life support. *Pediatric Critical Care Medicine* 2023;24:987–97.
59 Davis JS, Ryan ML, Perez EA, *et al*. ECMO hospital volume and survival in congenital diaphragmatic hernia repair. *J Surg Res* 2012;178:791–6.
60 Bucher BT, Guth RM, Saito JM, *et al*. Impact of hospital volume on in-hospital mortality of infants undergoing repair of congenital diaphragmatic hernia. *Ann Surg* 2010;252:635–42.
61 Lewit R, Jancelewicz T. Center volume and cost-effectiveness in the treatment of congenital diaphragmatic hernia. *J Surg Res* 2022;273:S0022-4804(21)00746-0:71–8:.
62 Lewit RA, Jancelewicz T. Sources of regional and center-level variability in survival and cost of care for congenital diaphragmatic hernia (CDH). *J Pediatr Surg* 2021;56:130–5.
63 Kays DW. ECMO in CDH: is there a role? *Semin Pediatr Surg* 2017;26:166–70.
64 Snoek KG, Reiss IKM, Greenough A, *et al*. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO consortium consensus - 2015 update. *Neonatology* 2016;110:66–74.

65 Puligandla PS, Skarsgard ED, Offringa M, *et al*. Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline. *CMAJ* 2018;190:E103–12.
66 Puligandla P, Skarsgard E, Baird R, *et al*. Diagnosis and management of congenital diaphragmatic hernia: a 2023 update from the Canadian congenital diaphragmatic hernia collaborative. *Arch Dis Child Fetal Neonatal Ed* 2023.:fetalneonatal-2023-325865.
67 Puligandla PS, Grabowski J, Austin M, *et al*. Management of congenital diaphragmatic hernia: a systematic review from the APSA outcomes and evidence based practice committee. *J Pediatr Surg* 2015;50:1958–70.
68 Sigalet DL, Tierney A, Adolph V, *et al*. Timing of repair of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation support. *J Pediatr Surg* 1995;30:1183–7.
69 Reyes C, Chang LK, Waffarn F, *et al*. Delayed repair of congenital diaphragmatic hernia with early high-frequency oscillatory ventilation during preoperative stabilization. *J Pediatr Surg* 1998;33:1010–4; .
70 Coughlin JP, Drucker DE, Cullen ML, *et al*. Delayed repair of congenital diaphragmatic hernia. *Am Surg* 1993;59:90–3.
71 Desfrere L, Jarreau PH, Dommergues M, *et al*. "Impact of delayed repair and elective high-frequency oscillatory ventilation on survival of antenatally diagnosed congenital diaphragmatic hernia: first application of these strategies in the more "severe" subgroup of antenatally diagnosed newborns". *Intensive Care Med* 2000;26:934–41.
72 Moyer V, Moya F, Tibboel R, *et al*. Late versus early surgical correction for congenital diaphragmatic hernia in newborn infants. *Cochrane Database Syst Rev* 2002;2010:CD001695.
73 Wilson JM, Lund DP, Lillehei CW, *et al*. Delayed repair and preoperative ECMO does not improve survival in high-risk congenital diaphragmatic hernia. *J Pediatr Surg* 1992;27:368–72; .
74 Hollinger LE, Lally PA, Tsao K, *et al*. A risk-stratified analysis of delayed congenital diaphragmatic hernia repair: does timing of operation matter. *Surgery* 2014;156:475–82.
75 Bryner BS, West BT, Hirschl RB, *et al*. Congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: does timing of repair matter. *J Pediatr Surg* 2009;44:1165–71.
76 Golden J, Jones N, Zagory J, *et al*. Outcomes of congenital diaphragmatic hernia repair on extracorporeal life support. *Pediatr Surg Int* 2017;33:125–31.
77 Robertson JO, Criss CN, Hsieh LB, *et al*. Comparison of early versus delayed strategies for repair of congenital diaphragmatic hernia on extracorporeal membrane oxygenation. *J Pediatr Surg* 2018;53:629–34.
78 Delaplain PT, Harting MT, Jancelewicz T, *et al*. Potential survival benefit with repair of congenital diaphragmatic hernia (CDH) after Extracorporeal membrane oxygenation (ECMO) in select patients: study by ELSO CDH interest group. *J Pediatr Surg* 2019;54:1132–7.
79 Stewart LA, Klein-Cloud R, Gerall C, *et al*. Extracorporeal membrane oxygenation (ECMO) and its complications in newborns with congenital diaphragmatic hernia. *J Pediatr Surg* 2022;57:1642–8.
80 Dassinger MS, Copeland DR, Gossett J, *et al*. Early repair of congenital diaphragmatic hernia on extracorporeal membrane oxygenation. *J Pediatr Surg* 2010;45:693–7.
81 Fallon SC, Cass DL, Olutoye OO, *et al*. Repair of congenital diaphragmatic Hernias on extracorporeal membrane oxygenation (ECMO): does early repair improve patient survival. *J Pediatr Surg* 2013;48:1172–6.
82 Dao DT, Burgos CM, Harting MT, *et al*. Surgical repair of congenital diaphragmatic hernia after extracorporeal membrane oxygenation Cannulation: early repair improves survival. *Ann Surg* 2021;274:186–94.
83 Glenn IC, Abdulhai S, Lally PA, *et al*. Early CDH repair on ECMO: improved survival but no decrease in ECMO duration (A CDH study group investigation). *J Pediatr Surg* 2019;54:2038–43.
84 Harting MT, Jancelewicz T. Surgical management of congenital diaphragmatic hernia. *Clin Perinatol* 2022;49:893–906.
85 Harting MT, Hollinger L, Tsao K, *et al*. Aggressive surgical management of congenital diaphragmatic hernia: worth the effort?: A multicenter, prospective, cohort study. *Ann Surg* 2018;267:977–82.
86 Steen EH, Lee TC, Vogel AM, *et al*. Congenital diaphragmatic hernia repair in patients on Extracorporeal membrane oxygenation: how early can we repair. *J Pediatr Surg* 2019;54:50–4.
87 Delaplain PT, Yu PT, Ehwerhemuepha L, *et al*. Predictors of long ECMO runs for congenital diaphragmatic hernia. *J Pediatr Surg* 2020;55:993–7.
88 Delaplain PT, Ehwerhemuepha L, Nguyen DV, *et al*. The development of multiorgan dysfunction in CDH-ECMO neonates is associated with the level of pre-ECMO support. *J Pediatr Surg* 2020;55:830–4.
89 Tiruvoipati R, Vinogradova Y, Faulkner G, *et al*. Predictors of outcome in patients with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation. *J Pediatr Surg* 2007;42:1345–50.
90 Kays DW, Islam S, Richards DS, *et al*. Extracorporeal life support in patients with congenital diaphragmatic hernia: how long should we treat? *J Am Coll Surg* 2014;218:808–17.
91 Danzer E, Harting MT, Dahlen A, *et al*. Impact of repeat extracorporeal life support on mortality and short-term in-hospital morbidities in neonates with congenital diaphragmatic hernia. *Ann Surg* 2023;278:e605–13.