The Management of Congenital Diaphragmatic Hernia in Infants with Extracorporeal Membrane Oxygenation: A Systematic Review

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Abstract. Congenital Diaphragmatic Hernia (CDH) is a rare birth defect in which the diaphragm fails to close during prenatal development, which causes the intestinal contents to herniate into the chest from the abdominal cavity causing lung hypoplasia and persistent pulmonary hypertension of the newborn (PPHN). Extracorporeal membrane oxygenation (ECMO) is a rescue therapy for infants having CDH on whom the conventional ventilation strategies fail. Our systematic review aimed to evaluate the outcomes of Extracorporeal Membrane Oxygenation (ECMO) use on infants with Congenital Diaphragmatic Hernia (CDH). We used PubMed, Embase, Web of Science and Google Scholars databases for our data collection, and articles from 2010-2021 were analyzed and included as part of this research. We included studies in the English language conducted on human infants. We excluded studies conducted before 2010, studies on animals, languages other than English, or studies conducted on the adult population from our research. We identified a total of 3650 studies from the databases. After removing duplicates, screening titles, applying inclusion-exclusion criteria, and assessing the papers' quality, we were left with nine articles. Six out of these nine articles were retrospective cohort studies, and three were literature reviews. We extracted data manually from these studies. ECMO's role in managing CDH in infants is controversial as some studies show improvements in infants' survival rate. In contrast, other studies mention that the risks involved in ECMO use outweigh the benefits, and we should only use it in those infants who are severely affected. Due to inadequate data, we require additional research to determine whether the use of ECMO is favorable or should it be discouraged.

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Keywords: Extracorporeal Membrane Oxygenation (ECMO), Extracorporeal Life Support, Congenital Diaphragmatic Hernia, Infants.

1. Introduction:

Congenital diaphragmatic hernia (CDH) is a congenital defect with a mortality rate ranging from 8% to 80% and occurs in one infant out of every 5000 births (Vaja et al., 2017). We can define congenital diaphragmatic hernia (CDH) as the failure to develop the diaphragm of newborns resulting from incomplete fusion of structures forming the diaphragm (McHoney, & Hammond, 2018). It leads to herniation of abdominal contents into the chest cavity causing impaired pulmonary development. High mortality in CDH is due to pulmonary hypertension, pulmonary hypoplasia, and other congenital anomalies (Grover et al., 2018). Neonates with CDH immediately after birth show signs of respiratory distress due to lung hypoplasia caused by the lungs' compression due to the herniated abdominal contents into the chest cavity (Bojanić et al. 2017). Advancements in technology have led to permissive hypercapnia, inhaled nitric oxide (iNO), high-frequency ventilation, and extracorporeal membrane oxygenation (ECMO) treatment of infants with CDH. The timing of surgical intervention has also changed from emergent perinatal surgery to delayed operation once the infant's condition improves (Hoffman et al., 2010). CDH is the most common noncardiac indication for neonatal ECMO (Grover et al., 2018).

Infants with Persistent pulmonary hypertension of the newborn (PPHN) and Pulmonary hypoplasia (PH) that do not respond to medical management are stabilized with Extracorporeal Membrane Oxygenation (ECMO) (Golden et al., 2017). ECMO provides recovery from a reversible respiratory failure by maintaining cardiac and pulmonary functions (Peter et al., 2020). Delivery of infants with a prenatal diagnosis of CDH should be in tertiary centers where early ECMO is available (Grover et al., 2018). According to the Extracorporeal Life Support Organization (ELSO) Registry's report, about 250-300 infants with CDH per year develop respiratory failure and receive ECMO (Peter et al., 2020). Extracorporeal life support

organizations reported that 50% of CDH patients survive, which has not improved over the past few decades (Okulu, et al., 2019).

There is a need for randomized controlled trials (RCTs) to clarify the picture about these patients' surgical management, appropriate timing and usage of ECMO, and short-term and long-term outcomes. An increase in ECMO use for more premature infants with improved anticoagulation use and the development of smaller cannulas and pumpless AV ECMO can also be seen in the future (Peter et al., 2020). In this systematic review, we aim to determine the role of ECMO in the management of Congenital diaphragmatic hernia. Figure 1 shows an infant with a diaphragmatic defect through which abdominal contents are herniated into the chest cavity compressing the infant's lung.

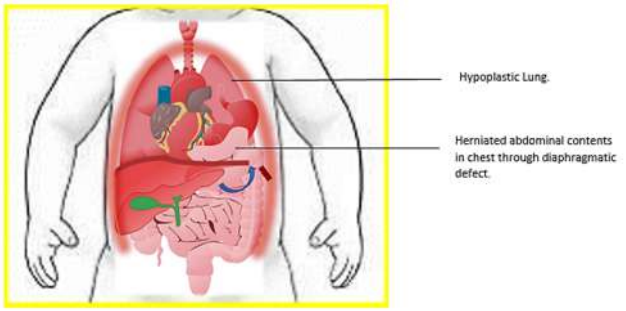

Figure 1: Infant with CDH showing herniated abdominal contents into the chest through the diaphragmatic defect.

CDH: Congenital Diaphragmatic Hernia.

2. Method:

2.1. Protocol

We obeyed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for conducting our systematic review (Moher, et al., 2009).

2.2. Sources of Data Collection

We used PubMed, Embase, Web of Science and Google Scholars to search for relevant studies for our data collection. We searched published data from 2010-2021.

2.3. Search Strategy

We used the following Medical Subject Heading (MeSH) strategy:

("Hernias, Diaphragmatic, Congenital / complications" [Majr] OR "Hernias, Diaphragmatic, Congenital/ diagnostic imaging" [Majr] OR "Hernias, Diaphragmatic, Congenital/mortality"[Majr] OR "Hernias, Diaphragmatic, Congenital/surgery"[Majr] OR "Hernias, Diaphragmatic, Congenital/therapy"[Majr]) AND (("Extracorporeal Membrane Oxygenation/adverse effects" [Majr] OR "Extracorporeal Membrane Oxygenation /instrumentation" [Majr] OR "Extracorporeal Membrane Oxygenation / methods"[Majr] OR "Extracorporeal Membrane Oxygenation/mortality"[Majr] OR "Extracorporeal Membrane Oxygenation /rehabilitation" [Majr] OR ("Extracorporeal Membrane Oxygenation /adverse effects"[Mesh:NoExp] OR "Extracorporeal Membrane Oxygenation/ instrumentation" [Mesh:NoExp] OR "Extracorporeal Membrane Oxygenation/methods "[Mesh:NoExp] OR "Extracorporeal Membrane Oxygenation /mortality" [Mesh:NoExp] OR "Extracorporeal Membrane Oxygenation/ rehabilitation" [Mesh:NoExp]))) AND (infants).

We used following keywords:

Extracorporeal membrane oxygenation OR ECMO OR extracorporeal life support AND congenital diaphragmatic hernia AND infants. We found a total of 3650 articles.

2.4. Inclusion Criteria

We included studies if they met the following criteria: (1) Papers published between 2010-2021. (2) Papers in English. (3) Studies conducted on human participants. (4) Studies that included infants.

2.5. Exclusion Criteria

We excluded studies containing: (1) Papers published before 2010 (2) Papers were in a language other than English. (3) Studies conducted on Animals. (4) Studies included the adult population. Figure 2 demonstrates the PRISMA flow diagram and steps taken in searching studies for our article.

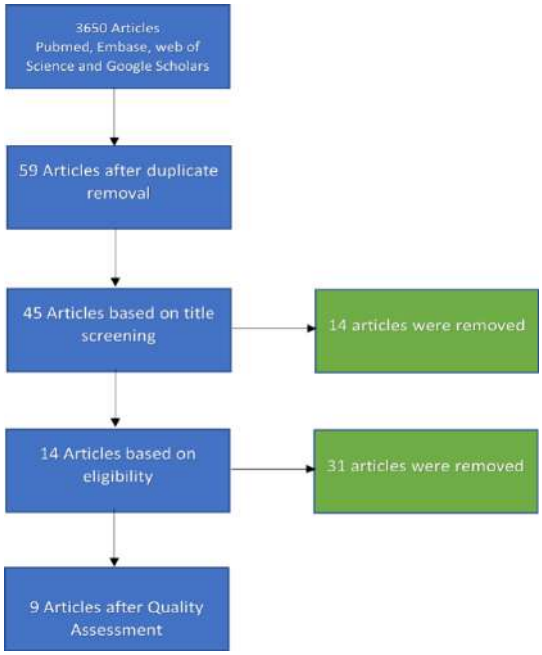

Figure 2. PRISMA Flow diagram

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3. Result

We identified a total of 3,650 studies from the databases from 2010-2021. Fifty-nine studies remained after the removal of duplicates. Forty-five studies remained after screening the titles of these 59 studies. Finally, 14 articles got selected after going through these studies' full text and applying inclusion and exclusion criteria. We assessed the quality of these 14 studies by using the quality assessment tools, and nine studies were shortlisted. Six out of the remaining nine articles were retrospective cohort studies, and three were literature reviews. In the end, we extracted data manually from these articles. We used the following quality assessment tools for the process mentioned above: SANRA = Literature Reviews.

New Castle Ottawa Tool = Retrospective Cohort Studies. In the following table, we have summarized the number of patients included in each study, the type of study conducted, each study's purpose, and the conclusions/ results obtained from each study. In Table 1, we have Summarized the Type, Number, and Purpose of the Studies Included in our Review and the Results/Conclusions Obtained from them.

4. Discussion

ECMO was used for the first time in 1977 in neonates with a congenital diaphragmatic hernia, followed by the surgical repair of CDH (Rafat, & Schaible, 2019; Peter et al., 2020) Neonates with CDH can either be asymptomatic or have mild or severe respiratory failure requiring ECMO (Hoffman et al., 2010). We, in our article, have focused on the neonates who had severe symptoms due to CDH and required ECMO. As the data available from RCTs and retrospective studies is still insufficient, ECMO's role in the management of CDH is still controversial (Okulu, et al., 2019; Kattan et al., 2010).

4.1. Indications, Contraindications and Time of Initiation of ECMO in Infants with CDH

4.1.1. Indications

Patients are considered for ECMO if they fulfill the following criteria: (a) OI>40 for 4 hrs (b) severe hypoxic respiratory failure with acute decompensation (PaO2<40mmHg). (c) failure of the neonate to achieve adequate oxygenation with preductal HbSO2 less than 85% despite optimal ventilation and pulmonary hypertension management. (d) mean airway pressure > 17 cm H2O (e) Oxygen delivery is not adequate with metabolic acidosis defined as lactate > 5 mmol/L and pH < 7.20 (e) Pulmonary hypertension with right ventricular dysfunction or progressive respiratory failure. (f) infant's weight > 2000gm. (g) gestational age >34 weeks. (h) no severe cerebral injury or any lethal anomaly (Rafat, & Schaible, 2019; Okulu, et al., 2019; Kattan et al., 2010).

4.1.2. Contraindications

ECMO is contraindicated in patients if: (a) They have fatal chromosomal abnormalities, congenital anomalies, uncontrolled bleeding disorder, Grade 3,4 intracranial hemorrhage. (b) body weight <2000gm. (c) Gestational age <34 weeks. (d) Prolonged high-pressure mechanical ventilation (Peter et al., 2020; Okulu, et al., 2019; Rafat, & Schaible, 2019).

4.1.3. Time of ECMO Initiation

There is not enough data available for the starting point of ECMO in a neonate with CDH. Many experts believe that it could be beneficial in treating patients with CDH as the pulmonary vasculature might be more responsive. Early treatment might reverse pulmonary artery hypertension, which can lead to right-sided heart failure (Rafat, & Schaible, 2019). Figure 3 shows how blood is circulated through an artificial lung by ECMO back to the bloodstream.

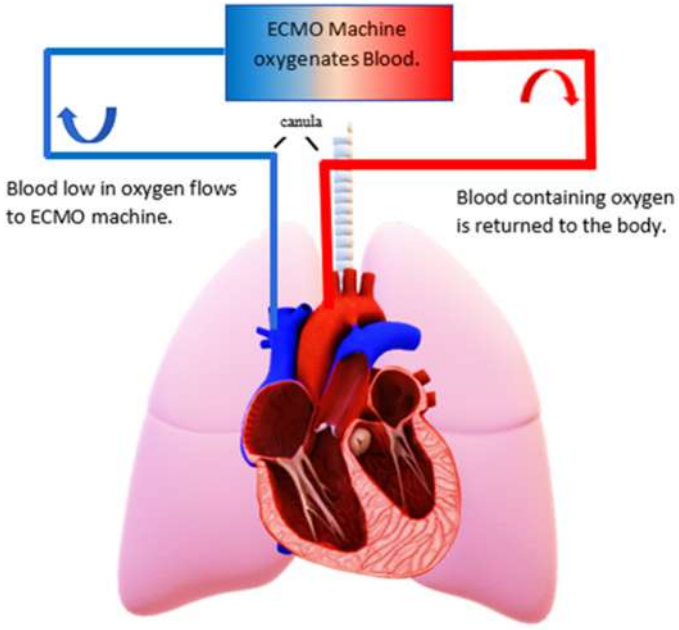

Figure 3. ECMO In Infants With CDH.

CDH: Congenital Diaphragmatic Hernia, ECMO: Extra Corporeal Membrane Oxygenation

4.1.4. ECMO Cannulation

There are two methods of ECMO in neonates with CDH to manage respiratory failure (a) Veno-venous (VV) and (b) Veno-arterial (VA) (Prabhu, et al., 2016). VA ECMO or VV ECMO's choice has not shown any difference to the survival rate, but the data available is poorly controlled (Kays, 2017).

Table 1. *Summarizing the Type, Number, and Purpose of the Studies Included in our Review and the Results/Conclusions Obtained from them.*

Author	Type of Study	No. of Patients	Study Purpose	Conclusion/Result
Hoffman et al. 2010	Retrospective cohort study.	62	To analyze the results and condition of infants with CDH receiving ECMO.	50% out of the 62 infants receiving ECMO survived.
Kattan et al. 2010	Retrospective cohort study.	46	To determine the results of the Neonatal ECMO program in NICU in infants with CDH.	ECMO program led to an increase in the survival of infants with CDH.
Okulu et al. 2019	Retrospective cohort study.	35	Compare survival rate of infants before and after the establishment of ECMO and its effect on infants' survival with CDH.	They did not see improvement in the survival rate of CDH patients after establishing the neonatal ECMO program.
Vaja et al.2017	Retrospective cohort study.	98	To determine the factors affecting survival outcome for repairing congenital diaphragmatic hernia with ECMO as a bridge to surgery and recovery.	If the patients survive the initial postoperative period, they have a good survival rate, and all infants with severe CDH should be offered ECMO.
Turek et al. 2017	Retrospective cohort study.	2500	To determine how the recent advancements have affected the survival rate of infants with CDH receiving ECMO.	In the modern era, the survival rate of infants with CDH receiving ECMO is dropping.
Prabhu et al. 2016	Retrospective cohort study.	6	Outcomes of ECMO on infants with CDH.	Survival is possible in cases involving severely compromised infants with CDH if they receive ECMO who would have died without its use.
Kays et al. 2017	Literature review	N/A	To identify the patients having CDH who are most likely to benefit from ECMO and how they can benefit from it.	ECMO benefits patients having CDH by improving the survival rate of those who are severely affected. But its risks outweigh the benefits in those who are less severely affected.
Peter et al. 2020	Literature review	N/A	To summarize the recent advancements in the management of CDH by ECMO.	The need for ECMO may decrease and could become obsolete in the future with recent advancements. But for now, it is a life-saving intervention.
Rafat et al. 2019	Literature review	N/A	To discuss the time to start ECMO and the timing of surgery.	ECMO's role in the management of CDH is controversial.

ECMO: Extra Corporeal Membrane Oxygenation, CDH: Congenital Diaphragmatic Hernia, NICU: Neonatal Intensive Care Unit.

VA ECMO involves cannulation of the right internal jugular vein (IJV) and right common carotid artery (CCA). VV ECMO constitutes placing a double-lumen (DL) cannula into the right internal jugular vein. VV ECMO is not possible if the smallest VVDL cannula cannot be placed in the internal jugular vein if the patient has an extremely poor cardiac function or extracorporeal cardiopulmonary resuscitation. Many prefer VA ECMO when the neonate is more critical (Peter et al., 2020).

According to ECMO Registries and some reports, VA ECMO may be beneficial if the neonate has severe cardiac dysfunction. According to reports, the incidence of seizure and intracranial bleeding is higher in patients receiving VA, while VV was associated with a higher incidence of poor renal perfusion (Rafat, & Schaible, 2019). Kays et al., in their review article, discussed the ELSO experience regarding this topic. They reviewed cases from 1991-2006. They found that during these 15 years, VA ECMO was used in 82% of infants, while 18% of infants used VV ECMO. There were no differences based on ECMO cannulation type in the survival rate of infants with CDH. According to reports, 18% of VV ECMO patients switched to VA ECMO, and the survival rate reduced from 54% to 44% after conversion compared to 50% when VA ECMO was started (Kays, 2017).

4.1.5. Timing of Surgical Repair of CDH

The time to perform the surgical repair of an infant's diaphragm with CDH has always been debatable. For decades emergency repair was considered necessary. It was thought that removing herniated abdominal contents from the chest was essential to improve respiratory distress. However, surgical repair caused lung compliance to worsen rather than improving. By the 1990s, delayed repair after a period of stabilization had become a widely accepted approach (Peter et al., 2020). Surgical repair while on ECMO increases the risk of bleeding (Rafat, & Schaible, 2019).

Turek et al. discussed that operating while the neonate is on ECMO will increase the risk of hemorrhagic and hematologic complications, negatively influencing patient outcomes. Their data suggested that repairs made after ECMO produced the best results. But there was a Bias because the neonates weaned from ECMO represented a healthier group. But a 75% survival for CDH surgical repair after successful weaning from ECMO would suggest that we should try at liberation from ECMO should be attempted before CDH repair whenever possible (Turek et al., 2017). A study in 2009 using data from the CDH group showed that when the defect was repaired on ECMO, the survival rate was 44%, whereas, after ECMO removal, the survival rate was 77%. But the potential for selection was not discussed by the authors. Patients having their defects repaired on ECMO needed more frequent patch repair and had lower 5-min APGAR scores that suggested worse disease than those weaned from ECMO unrepaired (Kays, 2017). Prabhu et al. stated in their study that CDH could repair safely on ECMO. According to them, early surgery on ECMO after a stable period of 12-24 hours decreases ECMO duration and complications and improves survival. They performed a retrospective study of six infants and had no intra-operative bleeding or clotting complications. One patient developed progressive communicating hydrocephalus and required a ventriculoperitoneal shunt before discharge. One patient developed cerebral palsy, but Magnetic Resonance Imaging (MRI) of the brain did not show any hemorrhage or infarction. None of these infants would have survived without ECMO. And they never attempted to withdraw ECMO before CDH repair (Prabhu et al., 2016).

A recent study by Vaja et al. suggests that the timing of repair did not affect the survival rate of the CDH patients. The repair in their study on ECMO showed twenty-two patients had postoperative bleeding requiring clotting factors administration, administration of antifibrinolytics changes in the heparin management, and surgical re-exploration. The majority of those patients who bled (90%) got repaired on ECMO. The bleeding was not associated with a significant difference in survival. Comparison between bleeding rates showed patients repaired on ECMO (24%) and off ECMO (11.8%) did not lead to any statistically significant difference on the independent sample t-test (P = 0.25) (Vaja et al., 2017).

The timing of repair of CDH with infants on ECMO is challenging to determine, and still more studies are required to determine the timing of repair of CDH in infants on ECMO, which will benefit the patients.

4.1.6. Follow-up

ECMO in CDH can lead to neurodevelopmental outcomes. For this purpose, an infant's cranial ultrasound should be done during the initial period to assess cerebral bleeding or infarction and long-term MRI evaluations, including angiography. Infant's memory, intelligence, and behavior should be evaluated, and echocardiographic investigations should be performed during school age. Moreover, lung testing should be performed to determine lung function development (Rafat, & Schaible, 2019). Kattan et al., in their study, did not find any severe developmental disabilities at 24 months follow-up in either group:0% (0/5) versus ECMO group 5% (1/20). One patient in the ECMO group developed cerebral atrophy and cerebral palsy after severe septic shock at nine months of age (Kattan et al., 2010). Prabhu et al., in their retrospective study, discussed the follow-up condition of the neonates that received ECMO during their CDH repair and at 12 months assessment, and all children (4) performed a low average range in the language assessment. One child performed in the average range in motor domains, one performed in the low average, and one in the extremely low range. In cognitive domains, two performed in the average range, one in the low average range, and one below-

average (Prabhu et al., 2016). A study showed that all the mortalities occurred within the first seven months from their ECMO discharge. There was no mortality in those patients, which suggested that if the infants survive initially, they may have better chances of survival (Vaja et al., 2017).

5. Limitations

Our research included studies from 2010-2021 that have limited our analysis on studies conducted before 2010. There was no randomized control trial in this duration that we could include in our review. All the included studies are retrospective. We did not have articles in other languages. Based on our review of studies, we suggest that all the neonates with a prenatal diagnosis of CDH should be born or transferred to neonatal intensive care with ECMO. All the studies are retrospective. There is a need for randomized control trials (RCTs) to gain more knowledge about ECMO's role in the management of CDH as the role is still controversial.

6. Conclusion:

In our systematic review, we aimed to determine ECMO's role in managing CDH in Infants. CDH leads to high rates of morbidity and mortality. There is not enough data available to choose the exact time of ECMO initiation or timing of surgical repair of CDH. The role of ECMO in the management of CDH in infants is controversial as some studies show an improvement in the survival rate of infants. In contrast, other studies mention that the risks involved in ECMO use outweigh the benefits and should be used in those infants who are severely affected. Further research, including randomized control trials (RCTs) and follow-up, is required to collect data further and assess the outcomes of ECMO on CDH as the data available from retrospective studies and literature is not enough to favor or discourage its use.

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Statement of interest:

All authors of this paper declare no conflict of interest related to this manuscript's content.

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