International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/

Vol. 50 No. 2 May 2025, pp. 17-48

Advancements In Understanding Congenital Diaphragmatic Hernia (Review)

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Abstract: Congenital diaphragmatic hernia (CDH) is a birth defect. It greatly impacts how the lungs and heart develop. Knowing about these defects, where they come from, and their effects matters for research. It also matters for improving CDH treatments. Recent studies in metabolomics and genomics have taught us more about CDH's causes. These studies suggest new ways to diagnose and treat the condition. Information on CDH is limited. Therefore, we reviewed existing research to gather data and offer insights into this uncommon disease. A better grasp of CDH's molecular basis could improve diagnosis and treatment. This may lead to better results for patients. Finding biomarkers is vital for early disease detection and risk assessment. This allows for quick recognition and proper care. A full literature review helps turn research into practice. It is a key step in using new, better methods to manage CDH patients.

Keywords: Congenital Diaphragmatic Hernia (CDH), pulmonary hypertension, prostaglandin E1, Patent Ductus Arteriosus (PDA), ventricular dysfunction, biomarkers.

I. Introduction

Congenital diaphragmatic hernia (CDH) is a rare birth defect. It affects the diaphragm. It occurs in about 2.3 out of 10,000 births [1]. A defect in the diaphragm's front and middle area causes CDH [2]. Abdominal organs shift into the chest cavity in CDH cases. This shift can include the stomach, intestines, or liver. Liver presence in the chest often means a worse outlook [2,3,4]. Other poor prognosis factors exist. These involve large defects and prenatal diagnosis. Left ventricle issues, heart defects, and right-sided CDH are risk factors. Low birth weight or hydrops fetalis also indicate risk [5, 6,7, 8, 9]. CDH is often an isolated problem. Yet, it can occur with heart, urogenital, or central nervous system issues [10,11]. Musculoskeletal or gastrointestinal anomalies are also possible. Chromosomal issues appear in 10–30% of cases [3]. Newborns with CDH show trouble breathing. This results from small lungs and high blood pressure in the lungs. These are key signs of the condition. CDH's main problems involve fewer alveoli and stiff airways. Thick artery walls, matrix changes, and high lung resistance also occur [11, 12, 13]. The causes of CDH are not fully clear. Both environment and genes play a role. Genetic causes include chromosomal problems and structural changes [14,15]. Copy number variants and single-gene mutations also contribute. Maternal age over 35 and male fetal sex raise CDH risk [1].

1. Pathophysiology of CDH

CDH often leads to varying lung hypoplasia. This usually affects both the ipsilateral and contralateral lung. This problem may begin around the 8th to 10th week of pregnancy [16]. It happens after the diaphragm fails to close as it should. Then, the separation of chest and abdominal organs does not occur. A "two-hit" idea explains lung hypoplasia. The first "hit," possibly genetic or

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 50 No. 2 May 2025, pp. 17-48

environmental, causes both lungs to develop poorly. This happens early in organ growth. The second "hit" is the hernia pressing on the lung itself [17]. Alongside lung changes are changes in blood vessels. The vessels mature early but are underdeveloped with more muscle [18]. This changes vessel tone and makes vessels smaller. Molecular pathways affect blood vessel changes in CDH. These pathways have been studied in humans and rat models [19]. They include retinol (20), VEGF [21], endothelin [22], BMP, and Apelin (23). Changes in these pathways can affect cells and signals to the lung's smooth muscle cells. Pulmonary arterial smooth muscle cell growth contributes to CDH-associated PH (CDH-PH). Hypertrophic pulmonary arterioles are characteristic of this condition [24]. Lung infants' development issues cause increased pulmonary vascular resistance and PH. Studies show over 70% of CDH have CDH-PH [25]. This is linked to higher mortality, oxygen needs at 30 days, and use of ECLS [26]. PH causes hypoxia from right-to-left shunting via the atria, patent ductus arteriosus, and any ventricular septal defect. It also increases afterload on the right ventricle (RV).The RV initially adapts by dilating, but may then hypertrophy and fail. A restrictive ductus arteriosus can worsen this. RV failure impairs left ventricle (LV) diastolic filling, reducing systemic blood flow. Myocardial ischaemia in the RV is key to heart failure in PH. Right coronary blood flow is compromised. In PH, the right coronary perfusion gradient falls due to increased RV pressures and decreased aortic pressures (from reduced LV preload and cardiac output) [27]. Reduced RV coronary perfusion, with increased myocardial oxygen use, can lead to RV ischaemia and dysfunction [28].

CDH is linked to structural and functional LV problems (29,30). Fetal LV hypoplasia is common, possibly from mechanical compression. Reduced fetal LV blood flow results from reduced pulmonary venous return and altered venous return streaming due to mediastinal shift [31–33]. An already hypoplastic LV faces increased afterload at birth. RV dilatation and dysfunction worsen this, leading to LV dysfunction and poor outcomes [34]. Patel et al. found that early LV systolic function correlated with disease severity markers [35]. Early PH management is vital to prevent biventricular dysfunction and impaired blood flow and oxygen delivery. Pulmonary hypoplasia, pulmonary hypertension, and ventricular dysfunction make CDH a complex challenge. CDH-PH treatment has focused on pulmonary vasodilation. Key targets are cytokine pathways that control pulmonary artery smooth muscle tone. These include the nitric oxide (NO), prostacyclin, and endothelin pathways [36].Inhaled nitric oxide (iNO) is a strong pulmonary vasodilator. It stimulates guanylyl cyclase in vascular smooth muscle cells, producing cyclic guanosine monophosphate (cGMP). High cGMP levels activate cGMP-dependent protein kinases and lower cytosolic calcium, relaxing smooth muscle [37]. Phosphodiesterases (PDEs) are enzymes that break down cyclic nucleotides (cGMP and cAMP). PDE inhibition causes vasodilation. PDE5 (a cGMP-specific PDE) and PDE3 and 4 (which break down cAMP) are in the lung [36]. Sildenafil, a PDE5 inhibitor acting via the NO pathway, is used for CDH-PH [38]. Milrinone, a PDE3 inhibitor, has been trialled in CDH cases. Prostacyclin is another pulmonary vasodilator. Epoprostenol and inhaled iloprost target this pathway. PDE3 inhibition reduces pulmonary arterial pressures via the PGI2 pathway. Endothelin (ET)-1 is a strong vasoconstrictor, making it a target for reducing pulmonary vascular resistance. Mohamed et al. found Bosentan, which acts on ETA and ETB receptors, superior to placebo for treating PPHN in neonates. This was shown in a randomised control trial.

2. Prenatal diagnosis

Finding the defect before birth and judging how bad it is are key. This guides later treatment and if intrauterine therapy is an option. Spotting patients with a poor outlook is vital. It allows talking about what therapy cannot achieve. Ultrasound can diagnose it in about 50–74% of cases. Most happen during a second-trimester scan [39,40]. Key signs on ultrasound include a fluid-filled stomach near or behind the heart. Also, a missing or partly missing pleural line, mediastinal shift, and an odd heart axis. Sometimes, the liver is in the chest. It can be hard to tell apart from lung tissue due to similar echoes. Using colour Doppler to view liver vessels and the ductus venosus can help. Polyhydramnios and hydrops fetalis may hint at a diaphragmatic defect. The key is to accurately assess how bad the defect is. Table 1 shows the ultrasound and MRI measures used for this.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 50 No. 2 May 2025, pp. 17-48

Table 1. Summary of the most frequently used ultrasound and MRI-based parameters in the assessment of CDH severity with their sensitivity and specificity for the prediction of survival and the need for ECMO (if available) [41-47]

		Sensitivity for the prediction of survival	Specificity for the prediction of survival	Sensitivity for the prediction of need for ECMO	Specificity for the prediction of need for ECMO
Ultrasound-based parameter					
LHR [48,49]	The ratio of the contralateral lung area- the product of the longest diameter of the lung and lung circumference via manual tracing, to the head circumference measured by ultrasound	0,67-0,89	0,43-0,57	0,52	0,73
o/e LHR [48,49]	The ratio of the observed LHR measured by ultrasound to the expected LHR obtained from data of normal fetuses at the same gestational age	0,49-0,98	0,13-0,83	0,70	0,55

L/T ratio [50]	The ratio of the area of the contralateral lung via manual tracing, to the area of the thorax defined as the space surrounded by the	0,75	0,92	–	–
	inner border of the bilateral ribs, the sternum, and the vertebra measured using ultrasonography of the transverse section containing the four-chamber view of the heart				
QLI [51]	Is obtained by the division of the contralateral lung area by a tenth of the head circumference.	0,87	0,75	–	–
Liver position [52]	Is expressed as a binary variable "up" (intrathoracic) or "down"	1 (for intrathoracic liver position)	0,48 (for intrathoracic liver position)	0,87 (for intrathoracic liver position)	0,51 (for intrathoracic liver position)

	(intra-abdominal); liver-up-defined as any part of the liver observed in the thorax space				
Stomach position	The presence of any portion of the stomach above the level of the diaphragm	–	–	–	–
MRI-based parameter					
TFLV [53]	Is obtained by tracing the region of interest around the	0,947	0,75	–	–
	left and right lung on each MRI slice, excluding the main vessels of the pulmonary hila. The sum of each slice area is then multiplied by				

	the slice thickness.				
o/eTFLV [48,49, 53]	The ratio of the observed TFLV measured by MRI to the expected TFLV obtained from data of normal fetuses at the same gestational age	0,77-0,87	0,48–1	0,82	0,57
PPLV [49]	Is calculated by dividing the actual lung volumes by the predicted lung	0,76	0,61	0,78	0,59
%LH [48,54]	volumes, multiplied by 100				
	Is calculated by dividing the hepatic volume above the diaphragm by the entire liver volume	0,73-0,80	0,78-0,91	0,58	0,91
LiTR [54]	Is obtained by dividing the herniated liver volume by the	0,64	0,91	0,42	0,88

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ISSN: 2509-0119.

https://ijpsat.org/
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	total chest volume				
MSA [53]	Is obtained at the level of a four-chamber view of the fetal heart. The first (sagittal) midline is drawn from the posterior face of the vertebral body to the middle of the sternum. The second line is drawn from the same point of the vertebral body to touch the lateral wall of the right atrium tangentially.	0,875	0,947	0,818	0,75

LHR means lung-to-head ratio. O/E LHR is the observed/expected lung-to-head ratio. L/T ratio means lung-to-thorax transverse area ratio. QLI is the quantitative lung index. TFLV is the total fetal lung volume. o/eTFLV means observed/expected total foetal lung volume. PPLV is percentage of predicted lung volume. %LH means liver herniation percentage. LiTR is the liver-to-thoracic volume ratio. MSA means mediastinal shift angle.

O/E-LHR, adjusted for how far along the pregnancy is, predicts mortality better than LHR alone. Most experts suggest a cut-off of ≤25% for left-sided CDH. A cut-off of <45% is suggested for right-sided CDH. These indicate severe pulmonary hypoplasia [55,56]. Liver herniation in the chest and how much liver is herniated are linked to worse outcomes. Fetal magnetic resonance imaging (MRI) is increasingly used to diagnose and assess CDH severity. MRI doesn't depend on the operator's skill. It isn't affected by the fetal position. Amniotic fluid levels or the mother's weight don't impact it. This makes it a better tool than ultrasound. It also helps to assess other malformations more accurately. However, MRI is not always available and is more expensive. This limits its routine use. The main factor for prognosis is o/e TFLV. Values below 25% indicate a severe condition. They strongly relate to postnatal outcomes [57,58]. In all CDH cases, checking the foetal heart before birth is vital. Around one-third of patients have heart

malformations. Ultrasound is the main tool for checking the foetal heart. Foetal MRI can offer extra useful information. Assessing the foetal heart with MRI has challenges. The foetal heart rate is high and can cause motion. Foetal structures are very small. ECG gating is needed. High-quality images are needed to see the foetal heart and major vessels well. Motion from the mother or foetus breathing, or needing a skilled doctor to read the study, makes cardiac MRI complex. Cardiac MRI is better after 30 weeks. Fetal heart structures are bigger then, and foetal movements are less common. This timing reduces MRI's usefulness. Key decisions about fetal care, like whether to use prenatal therapy, are often made earlier in pregnancy [59,60,61,62].

3. Prenatal approaches for the management of CDH

Fetal CDH can be managed by waiting or with FETO. FETO places a balloon in the fetal trachea. This prevents lung hypoplasia by trapping fluid and raising pressure. FETO is done at 26-28 weeks for severe cases and 30-32 weeks for moderate cases. The balloon stays until 34 weeks and is then removed using ultrasound [43,44]. A study compared waiting with FETO in severe left CDH cases. FETO had a 40% survival rate to discharge, while waiting had 15%. The six-month survival rate was similar. A similar study looked at moderate left CDH. FETO at 30-32 weeks led to 63% survival to discharge, while waiting led to 50%. At six months, 54% of infants in the FETO group and 44% in the expectant care group survived without needing extra oxygen. The relative risk was 1.23 (95% CI 0.93 to 1.65). Both studies showed a higher risk of premature membrane rupture in the FETO group. For severe CDH, it was 47% versus 11% (relative risk 4.51; 95% CI 1.83 to 11.9). For moderate CDH, it was 44% versus 12% (relative risk 3.79; 95% CI 2.13 to 6.91)[63,64,65]. The FETO group also had a greater risk of premature delivery. FETO shows some promise. However, it should be used with caution until more research is done. Prematurity from FETO may worsen outcomes for CDH patients. Steroid therapy should be given to fetuses at high risk of preterm birth before 34 weeks [66].

4. Multifaceted care strategies for CDH management

CDH requires varied care strategies. Delivery should occur after 39 weeks in a specialist centre. Caesarean sections offer no clear advantage over vaginal births [66]. This reduces hypoxemia by extending gas exchange. Postnatal care depends on lung failure, heart function, pulmonary hypertension, and ECMO availability. The CDH EURO Consortium guidelines (2016) suggest immediate intubation after birth [66]. But, babies with good prenatal lung development may breathe on their own. This prevents ventilator-induced lung injury. Standard ventilator support with low peak pressures (under 25 cm H2O) is advised [67,68,69]. Echocardiograms should be performed within 24 hours and repeated. Early ventricular dysfunction affects 39% of CDH cases. It is linked to higher mortality [70,71]. Routine surfactant use is not advised for CDH, regardless of gestational age [54,60]. Inhaled nitric oxide (iNO) is the main drug for CDH-PH, but its benefit is unclear. Some patients may respond. But recent reports show no better outcome in death and ECMO use. Identifying clinical phenotypes related to lung and heart issues is key when choosing treatments. Phenotypes are based on lung hypoplasia, pulmonary hypertension, and heart dysfunction. Pulmonary hypertension with good LV function may benefit from pulmonary vasodilation and gentle ventilation. Conversely, pulmonary hypertension with LV dysfunction may need inotropic support to boost LV output. They may not respond well to pulmonary vasodilators [72].

CDH patients need surgery to fix the diaphragm defect after birth. Surgery should be delayed until the patient is stable for the best results. The CDH study group's CDH(A-D) classification objectively stages patients by defect size. This is key for survival rate assessment and guides management and surgical choices. A "A" defect is small, allowing primary repair. A "D" defect means the diaphragm is almost completely absent, needing a patch [73]. Laparoscopic repair offers quicker recovery than open surgery. However, more research is needed via large trials to confirm its benefits, especially regarding recurrence risk. Tension-free repair is preferred, achieved in about 60% of cases. Larger defects often need a patch. Patch repairs increase hernia recurrence risk by 2.8 times, plus more complications like chylothorax and bowel obstruction [74-80]. For failed drug treatment and low oxygen levels, consider ECMO. ECMO is usually not for babies born before 34 weeks, weighing under 2 kg, or with certain abnormalities or brain bleeds [81-83]. Finally, newborns with CDH have special nutrition needs. They need enough nutrition. Aim for at least 125 kcal/kg/d and 2.3 g/kg/d of protein. This greatly affects their weight gain and brain development [84,85].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

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5. Pathoanatomical alterations concomitant with CDH

Understanding lung, bronchus, circulation, and heart changes helps grasp CDH better. The respiratory system starts developing early in pregnancy. Lung development continues after birth [86]. The reason for lung underdevelopment in CDH isn't fully clear. The "dual-hit" idea suggests two injuries cause it. The first affects both lungs before the diaphragm forms. The second affects one lung after the diaphragm defect, due to organs pushing through [87]. This reduces airway branching, causing smaller air sacs. There are fewer tiny airways and thicker lung walls. Animal studies suggest not enough lung coating, leading to immature lungs [88,89,90]. Changes in blood vessels are important. The vessel walls thicken, causing high blood pressure in the lungs. Lack of vessels and vessel changes cause persistent pulmonary hypertension in CDH [86,89,91]. This often resists standard treatments. A study compared blood vessel reactions in healthy and CDH placentas. Arteries affected by congenital diaphragmatic hernia (CDH) react differently than healthy ones. They constrict more to thromboxane A2 agonist. They dilate less to bradykinin and sodium nitroprusside. Fetoplacental and pulmonary arteries share similarities. However, the placenta lacks neuronal innervation, unlike the lungs. Studying fetoplacental arteries could predict responses to pulmonary treatments in CDH infants [92]. Autopsies of CDH patients and animal models show smaller hearts. The left ventricle, interventricular septum, and left atrium are reduced in size [93]. A study by Pelizzo et al. analysed heart tissue from fetuses with severe CDH. They found lower density of small arteries in the left ventricle. The interventricular septum had a higher density of these arteries. Vascular walls were thicker compared to controls. Small vessels penetrated the trabeculae, subendocardium, and papillary muscles, especially in the right ventricle [94].

6. Genetic causes of CDH

CDH can be an isolated defect or part of a genetic syndrome. Genetic alterations worsen the prognosis in both cases [95, 96]. Syndromes including CDH are Donnai-Barrow syndrome, syndromic microphthalmia, and Fryns syndrome [97]. Around 10–30% of CDH patients have chromosomal issues. These include aneuploidies and copy number variants (CNVs) [97]. CDH can occur with trisomy of chromosomes (13, 17, 18, 21, X, or monosomy of the X chromosome). Pallister-Killian syndrome, caused by tetrasomy of chromosome 12p, also relates to CDH. Common CNVs linked to CDH are 8p23.1 deletion and 15q26 deletion [97]. Schreiner et al. studied genetic anomalies in CDH patients with other malformations. They identified new CNVs affecting TUSC3 and PTPRD, which may contribute to CDH [98]. Next-generation sequencing (NGS) helps find new gene variants in CDH. This is useful when aCGH results are negative. Gürünlüoğlu et al. examined gene expression in CDH patients. They found 560 genes with altered expression. FOG2, SLC25A24, and WNT4 showed increased expression. Desmin and ALDH1 showed decreased expression. These genes relate to angiogenesis, lung development, and the retinoic acid pathway [99]. Kammoun et al. found variants in CDH-related genes like ZFPM2 and GATA4. They also found them in new candidate genes like TBX1 and PBX1 in fetuses with CDH.

Qiao et al. studied 827 CDH families. They found new gene changes that might cause CDH. LONP1 and ALYREF were named as possible risk genes. The LONP1 gene contributed to CDH with both new and rare harmful changes. Babies with rare, harmful changes in LONP1 had higher death rates. They also needed more ECMO support than others in the study[100].

7. The role of miRNAs in CDH pathogenesis

MicroRNAs (miRNAs) are now seen as vital in CDH. These small molecules regulate gene activity. They are found in fluids like blood and saliva. This makes them useful as biomarkers. Several miRNAs relate to lung growth. MiR-449a affects branching in human lungs. In mice, miR-127, miR-326, and miR-142-3p act in early lung growth. MiR-17, miR-20a, and miR-106b act later. The final stage involves miR-34a, miR-29b, miR-876-3p, and miR-421[101-110]. Research shows miRNAs impact lung vessel problems in CDH. This is key for pulmonary hypertension and chronic lung disease [111]. Herrera-Rivero et al. found seven miRNAs with different levels in CDH babies. These babies had chronic lung disease or died soon after birth. The changed miRNAs included let-7b-5p, −7c-5p, miR-1307-3p, −185-3p, −8084, −331-3p, and −210-3p. miRNAs regulate the cell cycle, inflammation, and morphogenesis. They act on molecules responding to growth factors, cytokines, and cell stress [112]. Fabietti et al. found different miRNA patterns in tracheal fluid of FETO survivors and non-survivors. Non-survivors had more mir-223-3p and mir-503-5p. Survivors showed higher mir-17-3p, mir-200b-5p, and mir-505-5p. Amniotic fluid from non-survivors had higher mir-379-5p and mir-889-3p [113]. Pereira-Terra et al. found more miR-200b and miR-10a in fetal lungs with CDH. miR-200b was also higher

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
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in those who responded to FETO [114]. Piersigilli et al. found more miR-16, miR-17, miR-18, miR-19b, and miR-20a in tracheal samples from CDH patients. miR-19 was about half as high in CDH patients [115]. In a rat model, prenatal miRNA therapy targeting miR-200b lowered CDH cases. Prenatal miRNA therapy is promising, but mostly used in animals now. Clinical use needs more research on safety and toxicity [116]. miRNA research in CDH could lead to new ways to diagnose and treat this condition.

8. Metabolomic profiling in the pathogenesis of CDH

Researchers are working to better understand CDH at a molecular level. They use genomics, transcriptomics, proteomics, and metabolomics. These methods can reveal CDH development pathways. Dobrinskikh et al. studied metabolic changes in a fetal rabbit model of left-sided CDH. They looked at changes after tracheal occlusion. CDH rabbits had a slower metabolic rate, especially in the left lung. Tracheal occlusion changed metabolic activity in both lungs. Fluorescence Lifetime Imaging (FLIM) showed differences in glycolysis, oxidative phosphorylation, and lipid signals between the lungs and groups [117].Romero-Lopez et al. used NMR to study metabolites in fetal rat lungs. Lactate, glutamate, and ATP changed the most between groups. They used ROC curve analysis to find metabolites that could be CDH biomarkers. Potential biomarkers included O-acetylcarnitine, AMP, ADP, UDP, UMP, and niacinamide.

Affected metabolic pathways showed changes in oxidative stress. This involved nicotinate, nicotinamide, ascorbate, aldarate, and glutathione metabolism. Nucleotide synthesis was disrupted, affecting pyrimidine metabolism. Aminoacyl-t-RNA biosynthesis and amino-sugar metabolism were also impacted. Amino acid metabolism showed changes, including glycine, serine, and threonine. Alanine, aspartate, glutamate, glutamine, histidine, arginine, and proline metabolism were affected. Glycerophospholipid and glucose metabolism also changed. This included pyruvate, the TCA cycle, and starch and sucrose metabolism [118].

Romero-Lopez et al. used H1 Nuclear Magnetic Resonance in a rat model. They looked at hypoxia and the bioenergetic status of fetal lungs. Nitrofen-exposed lungs had more hypoxia-inducible factor 1α (HIF-1α) and GLUT-1. HIF-1α is activated by hypoxia and ischemia. It helps switch from oxidative to glycolytic anaerobic metabolism. Hypoxia also boosts glucose transport into cells by increasing GLUTs. The AMP:ATP and ADP:ATP ratio was different from the control group. CDH lungs showed signs of energetic problems. Their energy charge was 0.15, while control lungs were 0.76. These metabolic changes could cause a bioenergetic collapse. This may affect lung hypoplasia and pulmonary arterial hypertension in CDH patients. More research is needed, like studies on mitochondria as a therapy target [119].Croitor-Sava et al. found different metabolic profiles in amniotic fluid. They compared fetuses with CDH to healthy fetuses. NMR spectroscopy could help find these differences earlier, aiding diagnosis. More research is needed to understand the clinical impacts [120].Metabolomics may improve CDH diagnosis and treatment, offering hope for better outcomes. Continued research and validation are essential for these advances.

9. Proteomics and CDH

Proteomic techniques can help us understand CDH better. They may also find new, cheap biomarkers. Wagner et al. studied the proteomic profile of hypoplastic CDH lungs in rats. They used Liquid Chromatography–Mass Spectrometry (LC–MS) at the alveolar stage (E21). They found 218 proteins with big changes between CDH and control lungs. These included Tenascin C, CREBBP, LYN, and STAT3.Tenascin C was less expressed near distal airway branches in CDH lungs. This was seen in both nitrofen-exposed and human fetal lungs. STAT3 expression was higher in the airway epithelium of nitrofen-exposed lungs at E21.Elevated levels of STAT3-related cytokines (IL-15, IL-9, IL-2) were found in tracheal aspirates from surviving CDH foetuses, compared to non-survivors. This suggests inflammation might contribute to abnormal lung development in CDH. Blocking STAT3 in foetal rat lung explants (E14.5) partially reversed hypoplastic lung development, showing increased lung budding ex vivo[121]. Tachi et al. identified 98 proteins with different levels in CDH umbilical cord serum versus healthy controls, using liquid chromatography–tandem mass spectrometry. Complement proteins C1q and C5 showed the biggest changes. Pathway analysis highlighted complement and coagulation cascades[122]. Xue Li et al. used Tandem Mass Tag (TMT) proteomics on foetal lungs in a CDH rat model, finding 79 proteins with different levels compared to controls. Some were linked to tight junctions, phospholipase D signalling, and the HIF-1 signalling pathway. Multiple tight junction proteins (Cldn3, Magi1, Myh9) were enriched in CDH foetal lungs. This suggests tight junction signalling affects impaired lung development in CDH[123]. Peiro et al. assessed the immune response in an ovine CDH model, finding changes in tracheal fluid samples. These included cell proliferation, PI3K/AKT/mTOR

signalling, inflammation, and microtubule dynamics. CDH suppressed cell proliferation and AKT signalling, while tracheal occlusion promoted these processes. Immune-related functions were mostly reduced in CDH samples versus controls. Downregulated pathways linked to interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling, cell cycle control, and the PI3K-AKT pathway. Upregulated proteins mainly involved immune-related pathways[124].

10. Non-omics approach to CDH

Omics methods are precise, identifying disturbed pathways and new targets. However, they are hard to implement in routine checks. Non-omics methods, like ELISA, are valuable. Omics methods (metabolomics or proteomics) study the entire metabolome and proteome. Non-omics methods assess one substance. Non-omics methods validate omics results for routine diagnostics. They are repeatable, common, cheap, and need less data analysis [125,126]. Several potential biomarkers for diagnosis, prognosis, and therapy have been reported. Growth factors and pro-inflammatory cytokines may affect vascular remodelling in pulmonary hypertension linked to CDH. Fleck et al. found lower levels of fibroblast growth factor-2 (FGF-2), macrophage-derived chemokine (MDC), and vascular endothelial growth factor (VEGF) in plasma from mothers carrying fetuses with CDH. Researchers also found that newborns with CDH had higher levels of several substances in their cord blood. These included epidermal growth factor (EGF), eotaxin, interleukin-3 (IL-3), and macrophage inflammatory protein-1β (MIP-1β). Platelet-derived growth factor-AA (PDGF-AA) and interleukin-1α (IL-1α) were also elevated compared to control subjects [127]. Similarly, a study by Patel et al. looked at VEGFA and placental growth factor (PLGF) in CDH newborns. They assessed how these factors related to pulmonary hypertension severity. Higher VEGFA and lower PLGF levels linked to more severe pulmonary vascular disease. Infants who did not survive showed a higher VEGFA:PLGF ratio than survivors. This was seen on days 3–4 and during the second week of life [128]. Okawada et al. found that high levels of monocyte chemotactic protein-1 (MCP-1) may promote pulmonary hypertension in CDH [129]. MCP-1 is a chemokine produced by various cells. These findings suggest new biomarkers for pulmonary hypertension in CDH. Prenatal treatments targeting inflammation could help these patients.

Oxidative stress may also play a role in pulmonary hypoplasia and pulmonary hypertension in CDH. Dingemann et al. found higher levels of platelet-derived growth factor receptor α (PDGFRα) and platelet-derived growth factor A (PDGFA) in fetal rat lungs. PDGFA and PDGFRα are important for lung growth. They can trigger the production of H2O2, which changes the cell's redox state. This may contribute to pulmonary hypoplasia in CDH [130]. Pulmonary NADPH oxidase 4 (Nox4) is found in smooth muscle and endothelial cells of blood vessels. It produces superoxide in the vessels. Increased Nox4 activity is linked to human pulmonary hypertension. Peroxisome proliferator-activated receptor (PPARγ) is the main regulator of Nox4 expression. Activating PPARγ can reduce Nox4 production and lessen pulmonary hypertension in lab models [131]. Gosemann et al. found higher Nox4 levels and lower PPARγ levels in nitrofen-induced CDH compared to controls. This supports the idea that oxidative stress is involved in the disease [132].

Problems in the PPARγ pathway may result from issues with RAGE signalling and lower levels of sRAGE. These factors affect pulmonary arterial smooth muscle cell growth and vascular changes. High RAGE expression in pulmonary arterial smooth muscle cells reduces PPARγ pathway activity. This has been shown in animal models and confirmed in CDH newborns. Hofmann et al. found more RAGE gene and protein expression in the pulmonary vessels of nitrofen-induced CDH. This suggests that elevated RAGE expression may contribute to pulmonary hypertension in nitrofen-induced CDH animal models. Kipfmueller et al. also conducted a study. sRAGE levels strongly correlated with PH severity, mechanical ventilation intensity/duration, and prenatal CDH markers. These markers include lung size and liver herniation, as shown in a neonatal CDH study. CDH newborns with sRAGE below 650 pg/ml at birth had a five times higher chance of needing ECMO. Those with sRAGE above 3500 pg/ml at 6 hours post-birth had a nine times higher chance. This suggests sRAGE's role in CDH pathophysiology, making it a potential treatment target. sRAGE could also mark CDH severity[133,134]. Future studies on antiproliferative treatments targeting altered cellular redox homeostasis may prove fruitful.

Endothelial progenitor cells (EPCs) are key in vascularisation. Baker et al. found increased and highly proliferative cord blood endothelial colony-forming cells (ECFC) in CDH newborns [135]. Fujinaga et al. support EPC involvement in CDH, noting a smaller ECFC population with impaired function in CDH neonates. However, these results contrast Baker et al.'s findings.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

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Pulmonary hypoplasia in CDH might relate to impaired ECFC functions. ECFCs could be a novel biomarker and therapeutic target for CDH. More studies are needed on EPC functions in CDH lung development[136].Schroeder et al. proposed carbohydrate antigen 125 (CA125) as a new cardiac biomarker for CDH severity assessment in a study of sixty-eight infants. CA125 values were higher in infants needing ECMO and those who did not survive. CA125 values also correlated with pulmonary hypertension severity and ventricular dysfunction markers [137]. CA125 can help identify high-risk infants early. It may also guide ECMO decisions or infant transfers to specialised centres. This may improve clinical management of CDH newborns. Future trials should analyse CA125 as a biomarker.

11. Prenatal management

Prenatally diagnosed CDH often has additional structural and genetic issues (30–40%), mainly cardiovascular malformations. All antenatally detected CDH cases require a detailed anatomical survey and fetal echocardiogram at a tertiary centre. Invasive genetic testing with chromosomal microarray analysis (CMA) should be offered due to a 10–13% risk of CMA abnormality in isolated CDH. Expanded genomic analysis may further increase diagnostic yield.

11.1 New recommendations regarding prenatal diagnosis and management of CDH

Antenatal sonographic predictors of neonatal survival include the observed-to-expected lung-to-head ratio (o/e LHR) and intrathoracic liver herniation. The o/e LHR should be measured with the trace method between 22- and 32-weeks' gestational age in experienced centres. In left-sided CDH, an observed-to-expected lung-to-head ratio (o/e LHR) of ≤25% suggests severe pulmonary hypoplasia. For right-sided CDH, this threshold is ≤50%. Survival rates are estimated at ≤30% and 20% for left and right CDH, respectively. Moderate pulmonary hypoplasia in left CDH is indicated by an o/e LHR of 26–34%. Detecting liver herniation in the chest using ultrasound can be difficult. Therefore, classifying stomach position has been suggested as a substitute marker. Stomach position correlates with newborn death and illness. This simple predictor shows promise, but needs more testing. Fetal MRI gives extra details for prognosis by checking total fetal lung volume and liver herniation. An o/e TFLV below 35% and liver herniation inside the chest predict mortality. MRI is more consistent than ultrasound. It isn't affected by the mother's size or the baby's position. MRI also predicts survival better, with more accuracy. Based on the TOTAL trial and current practice, 26 weeks seems ideal for MRI. Earlier scans might be wrong. Together, o/e TFLV and liver herniation better predict mortality and need for ECLS. MRI helps with prenatal prognosis, but ultrasound is still key due to its availability. Both scans should be used, especially for high-risk babies. Delivery should be at a specialist centre with a NICU and paediatric surgeons for CDH. Deliveries outside such centres increase mortality. The delivery method follows normal obstetric rules. Delivery should be considered around 38 to 39 weeks. This timing may improve survival at 28 days.[138-148]

11.2 Fetal therapy in CDH

Due to CDH's risks, fetal treatments try to boost lung growth in the uterus. Fetal endoscopic tracheal occlusion (FETO) is a key procedure. It's minimally invasive. FETO stops fetal fluid leaving, which speeds up airway and lung growth. Studies show FETO improves survival for left and right CDH. The TOTAL trials studied FETO's impact on survival in isolated left CDH. This included cases with moderate (o/e LHR 25–35% or o/e LHR 35–45% with liver herniation) and severe (o/e LHR <25%) lung problems. They compared FETO with standard care. The 'severe' trial showed FETO, done at 27–29 weeks, improved survival to discharge (40% vs 15%; p=0.009). However, it raised the risk of premature rupture of membranes (PPROM; 47% vs 11%) and preterm birth (75% vs 29%). The 'moderate' trial used later FETO at 30–32 weeks. It also saw more PPROM (44% vs 12%) and preterm birth (64% vs 22%). Survival didn't improve (63% vs 50%; p=0.06). Combining data from both trials showed the results varied by o/e LHR and gestational age at balloon insertion. The trial differences likely came from later balloon insertion in the moderate trial.

11.2.1 New recommendations regarding fetal therapy in CDH

FETO might help infants with severe, and some moderate, CDH. More research is needed for moderate CDH cases. FETO decisions should involve families. Consider the burdens, maternal risks, and travel. FETO is only available at select centres. This can disrupt family support, work, and income. Further studies are needed. These should assess how prematurity impacts outcomes after FETO.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
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Sildenafil to prevent pulmonary hypertension shows promise. Animal studies suggest it can improve lung development. Trials are testing sildenafil's safety in humans. This may lead to a trial of sildenafil for pulmonary hypertension.[149-153]

11.2 Ventilation in CDH

Newborns with CDH should have immediate intubation. Avoid bag-valve-mask ventilation. Some infants with mild CDH can breathe on their own. A small study found this worked in 40% of cases. However, half needed non-invasive ventilation. This carries a risk of organ issues. Survival and ventilation time were similar, regardless of breathing method. Current guidelines do not need changing based on this.

11.2.1 Ventilation Mode

The VICI trial studied ventilation methods in CDH. It compared conventional ventilation (CMV) to high-frequency oscillatory ventilation (HFOV). Mortality and lung issues were similar in both groups. This trial analysed 171 of 356 patients. Two studies compared conventional and high-frequency ventilation (HFV). They found no difference in survival or need for nitric oxide. Ventilation time and oxygen needs were also similar. One study was at a non-ECLS centre over 25 years. The HFV group used both jet ventilation and HFOV. Another study compared HFOV to CMV. Doctors likely used HFV for sicker patients in both studies. Single-centre studies suggest other ventilation methods might help. These include high-frequency positive pressure ventilation and neurally adjusted ventilatory assist. Heliox with oxygen also shows promise.

11.3 Fundamentals of haemodynamic support

In haemodynamic instability, treatment focuses on careful fluid use. Early inotropic support helps prevent pulmonary edema. Ventricular dysfunction worsens hypotension and is made worse by too much fluid. The inotropic agent depends on the baby's condition. Dopamine, epinephrine, or norepinephrine are often the first choices. High doses of epinephrine may cause heart problems, high blood sugar, and lactic acidosis. This results from a shift from beta to alpha-receptor agonist effects. Norepinephrine only affects blood vessels. It can increase afterload and harm heart function. It may also raise pulmonary arterial resistance. Some data suggest dopamine is not the best choice. This is based on its use in babies without CDH who have persistent pulmonary hypertension. Dopamine remains a common inotropic drug in neonatal care. It has a good safety record. There are no solid proof other drugs are better than dopamine for CDH. Vasopressin shows promise for catecholamine-resistant shock. It supports systemic haemodynamic without impacting pulmonary haemodynamic, according to a small study. Cardiovascular management requires careful agent selection and dosing. Treatment must be tailored to each baby's needs and cardiovascular status.

11.3.1 Unchanged recommendations regarding the fundamentals of haemodynamic support in CDH

Evidence shows cardiovascular issues vary among CDH patients. These problems can change quickly after hospital admission. This highlights the need for constant monitoring and bedside echocardiography. Although different cardiovascular issues exist, trials have not shown the best treatments. There is no evidence for acute pulmonary hypertension or ventricular dysfunction in CDH. Clinicians should base treatment on their assessment of the baby's physiology. Acute kidney injury (AKI) is defined using specific serum creatinine criteria. Studies show AKI is common in babies with CDH. Survival rates with AKI range from 37% to 47%. A higher AKI stage links to lower survival. AKI in CDH is linked to prenatal and postnatal risk factors. These include low antenatal lung volumes and liver herniation. Postnatal factors involve vancomycin, corticosteroids, diuretics, surgery, hypotension, and high plasma-free haemoglobin. The situation is harder in babies on ECLS. They are prone to fluid overload and systemic inflammation, which can cause AKI. Unstable babies should receive hydrocortisone and echocardiography for heart function assessment. This applies if they do not improve with fluid and vasopressor therapy.[154,155]

11.4 The role of echocardiography in CDH

Echocardiography plays a key role in managing CDH. It is advised soon after birth. It checks for heart defects and assesses heart function. It also estimates lung artery pressure and shunt flow. This helps guide heart support. At least two standard echocardiograms are recommended. The first occurs within 24–48 hours, or before surgery. Earlier scans are needed for high-risk infants or unstable patients. This can affect treatment and surgery timing, especially for ECLS [156,157]. Some studies delay the first scan to avoid

excess handling. A second scan should happen at 2–3 weeks. It checks for ongoing lung hypertension or heart issues. More scans may be needed if problems arise. This is vital with lung hypertension or heart problems. These issues can affect surgery and anaesthesia [158-160]. Two studies show PAAT/ET may help assess early risk. Lower PAAT/ET values link to ECLS and worse outcomes. Echocardiography at 5–7 days during ECLS may be helpful [161,162].

11.4.1 New recommendations regarding the use of echocardiography in CDH

BNP levels can also help detect heart strain. Rising BNP levels link to poor CDH outcomes. However, BNP testing availability varies. There is little proof that BNP monitoring alone improves outcomes. Prostaglandins may help manage lung hypertension in CDH. Two small studies looked at PGE1's impact. PGE1 improved oxygen levels and ductal blood flow. It also lowered inspired oxygen needs. Another study showed better echo results and lower BNP levels with PGE1. Both support PGE1 use for restricted ductus arteriosus, severe lung hypertension, and right heart failure.[156-165]

11.5 Updated recommendations regarding the role of prostaglandin E1 (PGE1) in the medical management of pulmonary hypertension associated with CDH

Targeted pulmonary vasodilation is also recommended. Use it when standard treatments fail to maintain oxygen or heart function. Inhaled nitric oxide (iNO) may be considered if echocardiography and clinical signs show improvement. If no improvement is seen, iNO should be stopped. Milrinone can help the left ventricle. It also widens blood vessels in the lungs and body while improving diastolic function. It is excreted by the kidneys. Milrinone is used to widen lung blood vessels. This is based on experience with infants who have pulmonary hypertension, but not CDH. Use caution if the patient has low blood pressure. A study is ongoing to clarify milrinone use in CDH patients. Prostaglandins (treprostinil, epoprostenol) and vasopressin can be rescue therapies for pulmonary hypertension in newborns with CDH. This can occur before, during, or after ECLS. Some patients respond to these therapies. However, do not delay other life-saving treatments like ECLS for severe respiratory failure if criteria are met.[166-167]

11.6 New recommendations regarding targeted pulmonary vasodilation in the management of CDH-associated pulmonary hypertension

11.6.1 The role of ECLS in the management of CDH

The Extracorporeal Life Support Organization (ELSO) recently released guidelines. They did not clearly follow GRADE methods. ELSO made 26 recommendations for CDH management. Many overlap with the recommendations here. This group supports ELSO's advice for starting ECLS. This includes respiratory failure, circulatory failure, or clinical decline. Evidence is still limited that ECLS improves survival in CDH. One large study showed higher overall mortality with ECLS. A survival benefit was only seen in high-risk patients at high-volume centres. This suggests ECLS might lower mortality in high-risk CDH patients. Two recent studies argue against long ECLS runs due to cost. Current age (<34 weeks) and weight (<1.7–2 kg) limits for ECLS are being reconsidered. A review of premature babies on ECLS showed similar survival rates for those with and without CDH. The latest ELSO data shows 50% overall survival (n=7564). Survival is slightly lower in infants <34 weeks (44%). It is even lower in those <2 kg (29%). ECLS in these groups has high risks of death and brain damage. Therefore, ECLS for CDH patients with these contraindications should be experimental. It should only be done at high-volume ECLS centres. Two recent studies reviewed repeat ECLS for CDH (n=31). Both supported it. Cannulation criteria were like those used initially. CDH patients on ECLS have worse developmental outcomes. It is unclear if a second run makes this worse. Surgical repair should be delayed until the baby is stable. Stability means good heart and lung function, plus enough oxygen to avoid problems. This approach seems to improve outcomes for babies with CDH. A study looked at 158 babies with CDH and oxygen levels. It found that oxygen levels in the first 24 hours could help decide when to operate. An oxygen index (OI) below 9.4 meant better survival. Waiting to operate after the OI was below 9.4 led to more time on the ventilator. It also meant a longer stay in the hospital. So, there's no benefit to delaying surgery after the baby is stable. Another study of 30 babies found the same thing. Delaying surgery past 48 hours didn't help babies with mild-moderate CDH.

More research shows that survival is possible even in high-risk cases. It is important to repair the CDH if possible. A study looked at hospitals with different success rates. Hospitals that repaired more babies had better survival rates. This suggests even the sickest

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
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babies can survive with surgery. If the defect is too big for a direct repair, a patch is needed. There's no best patch material, either synthetic or biological. Some studies show success using muscle flaps from the baby. Two studies looked at 97 babies who had large defects closed with muscle flaps. They found low recurrence rates after 5 years, around 3%. Repair rates were similar for those on ECMO, compared to patch repair. Complications were also similar. Other studies reported similar results with muscle flaps. Long-term problems like scoliosis were the same in both groups. Minimally invasive surgery has a higher chance of recurrence than open surgery. It's important to choose patients carefully. Pick those with good lung function and low blood pressure in the lungs. Five studies looked at 137 patients. They found recurrence rates of 7–21% after keyhole surgery. Using a biological mesh underlay may lower the risk of recurrence. It may also reduce the risk of bowel obstruction.[165,168.169,170,171]

12. Updated Surgical Repair Recommendations for CDH

A study of 37 infants having tracheal repair found a link between preoperative OI >3 and treatment failure. Treatment failure meant needing conversion or serious complications after surgery [172-177].

12.1 Surgical Repair During ECLS

About 50% of CDH infants needing ECLS survive to discharge. Some centres report survival rates near 70%. Repair complications during ECLS mainly involve metabolism, the circuit, or bleeding, which includes the surgical site, happens in 25% of cases. Surgical methods and adjusted anticoagulation only partly reduce this risk. Around 15% of infants on ECLS do not get CDH repair. Repair during ECLS could lower this rate [178,179]. Two registry studies examined how CDH repair during or after ECLS affects survival. One study showed that repair during ECLS improved survival[180]]. However, this benefit disappeared when non-repairs were excluded. Another study showed that repair during ECLS increased mortality threefold. It also found a higher risk of severe neurological injury. A study showed the best survival rate (94%) in infants decannulated before repair [181]. Studies on early versus late repair during ECLS have varied results. Some studies showed better survival with early repair (less than 72 hours) [179-182]. A study showed improved survival when repair occurred within 24 hours of cannulation [183]. But, another study found that early repair (≤5 days) predicted higher mortality[181].

A study reported on the neurocognitive results after 2 years in CDH survivors repaired on ECLS versus after or without ECLS. The entire CDH group had lower neurocognitive scores than normal. The group repaired on ECLS had lower cognitive and motor scores than those repaired after ECLS[184].These results suggest that the connection between survival and repair timing with ECLS is affected by whether non-repair mortality is included. Patients with bad prenatal signs who need ECLS are at the highest risk of non-repair. Early repair should be considered for these patients.

12.2 Managing Gastro-Oesophageal Reflux in CDH

GERD is very common. Testing shows GERD persists in over 60% of CDH infants after 1 year [185]. Some considered "preventative" fundoplication. A study looked at preventative fundoplication versus no fundoplication for high-risk cases during CDH repair. Redo fundoplication was more frequent in the preventative group. This was when compared to later fundoplication for GERD that did not respond to medication in the no fundoplication group[177]. Preventative fundoplication led to longer hospital stays. It also caused more problems, such as oral aversion. Some patients needed tube feeding for over six months. Fundoplication at CDH repair offers no benefit. Consider it only if medical treatment fails.

12.2.1 Updated recommendation regarding the management of gastro-oesophageal reflux in CDH

Studies continue to explore the long-term effects of CDH. These extend beyond the initial NICU stay. They include cardiopulmonary[186-194], gastrointestinal/nutrition/growth [190], and neurodevelopmental issues[195-199]. Musculoskeletal problems[184.191,195,200,201,202,203] and late mortality [204]are also concerns. These findings highlight the need for long-term follow-up. A team with CDH expertise should provide this care. Follow the guidelines from the American Academy of Pediatrics. Transitioning CDH patients from child to adult care is another area needing more study.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

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12.3 Updated and new recommendations regarding long-term follow-up in CDH

Guidelines exist for pain relief and sedation in infants needing ventilators. These apply to CDH patients with severe breathing problems. First, use a pain score[205] to adjust opioid doses. This is a strong recommendation. Second, fentanyl is better than morphine if there is low blood pressure or kidney failure. This is a conditional recommendation[206]. Third, switch opioids if tolerance develops. This is another conditional recommendation. Fourth, short-acting benzodiazepines can lower opioid or muscle relaxant needs. This is also a conditional recommendation. Fentanyl infusions have good results and similar pain scores to bolus doses [207].

12.4 New recommendations regarding pain, analgesia and neuromuscular blockade management in CDH

Evidence supports using intravenous and enteral acetaminophen or paracetamol after CDH surgery. The Children's Hospital Neonatal Consortium (CHNC) CDH Database[208] shows it was used in 48% of post-repair patients. A review showed that paracetamol reduced opioid use in infants after painful procedures or surgery[209]. Studies show that paracetamol combined with opioids after non-cardiac surgery reduces opioid use and has similar pain scores compared to a placebo[210,211]. A quality improvement study showed that a protocol using intravenous acetaminophen, education, and pain handover reduced opioid use and intubation time in CDH patients[212]. Little evidence exists on using muscle relaxants for pre-operative stabilisation in CDH infants. A study of 15 ventilated CDH infants showed that pancuronium decreased lung compliance. Also, a registry review found that prolonged sedation and muscle relaxation led to longer stays and higher death rates. The CHNC Database showed muscle relaxation was used nearly twice as often in non-survivors versus survivors before repair (87% vs 48%)[205.206,207,208,209,211,212].

12.5 Predisposing Factors for Recurrence

Many predisposing factors (PF) in pre- and postnatal life have been studied. These include congenital and acquired diseases, plus medical and surgical issues. Results across studies remain varied.

12.5.1 Prenatal

Some authors found no difference in recurrence rates based on prenatal factors[213]. However, most studies report higher recurrence with signs of larger defects. These signs include a lower observed/expected lung to head ratio (O/E LHR%). Other signs are prenatal CDH diagnosis before 22 weeks and observed/expected total fetal lung volume (O/E TFLV) under 30%. Thoracic liver position is another indicator [214-218]. Amodeo et al. found recurrence-prone patients have lower final O/E LHR% during fetal life. They could be identified early after birth using chest X-rays (CXR) to estimate lung surface area. Each cm2 increase in total and ipsilateral area reduced recurrence risk by 14% and 29%, respectively[217]. This suggests recurrence links to defect size. Large defects also associate with early in-hospital recurrence. A missing hernia sac is another prenatal risk factor[218-220]. Evidence on right-sided defects is mixed[221,222]. Fetal Endoscopic Tracheal Occlusion (FETO) is not a confirmed risk factor for recurrence[217,221,223].

12.5.2 Postnatal

Several postnatal PFs seem recurrence-related. Some may indicate larger defects. Examples are needing ECMO and using diaphragmatic and abdominal patches. Others link to disease severity. These include long invasive respiratory support, intensive care, and extended mechanical ventilation. Post-operative sildenafil needs, longer hospital stays (LOS), and discharge age are also factors. Supplemental oxygen needs and persistent pulmonary hypertension matter too. Some factors, like thoracotomy and MIS, relate to surgical choices[217,224,225,226,227].

Surgical-related PFs seem key in postnatal recurrence. Patch use, both diaphragmatic and abdominal, is significant. Despite this, patch use has increased recently. Diaphragmatic patch repair patients have a 2.83 times higher recurrence risk[228]. Synthetic patches cannot grow with the patient, explaining this link[223]. Disease severity and defect size may also play a role[228]. Patches close defects without tension, despite large size, allowing a tension-free suture. This aims to cut recurrence risk, and Zahn et al. [229]suggest it is effective. Another benefit is creating an "over-sized" cone shape for the new diaphragm. This allows better respiratory function, giving the thoracic cavity a more normal shape and volume. It also provides extra abdominal volume during

the first year's growth, helping tissue growth. Yet, some studies show no recurrence rate difference between patch and primary repair. Others even report lower recurrence with patches. This contrasts with large series data from high-volume centres.

Intraoperative imaging guides patch repair. Dome-shaped and cone-shaped patch repairs exist[230]. Patch material choice remains an open question. A recent study suggests non-absorbable PTFE patches have lower recurrence rates than absorbable SIS patches. This study's follow-up was limited, affecting the comparison of PTFE and SIS patches. Despite limitations in Camila et al.'s study, PTFE patches show promise. Alternatives to diaphragmatic patches exist. Muscle flaps, like the reversed latissimus dorsi, can close breaches. These flaps are suggested for large defects or hemidiaphragm agenesis. Limited data show similar or better results with muscle flaps. More extensive studies are needed to confirm this. Strong evidence is lacking. Muscle flaps lack innervation, which can cause diaphragm dysfunction in significant defects.

Researchers constantly seek the "perfect" graft for diaphragmatic repair. Tissue-engineered diaphragmatic repair is a promising area. Current evidence supports using non-absorbable prosthetic patches, mainly PTFE. Aiming for an oversized, dome shape is also recommended. PTFE appears safe and reduces recurrence. Using an abdominal patch is another surgical problem. Even if removed quickly, it can cause recurrence. This happens by disrupting the diaphragm's link to the abdominal wall. Most surgeons agree that surgical technique impacts recurrence. The postero-lateral defect section needs careful attention. Secure the patch around the ribs and intercostal muscles if needed. A non-resorbable suture usually secures the patch. Pledged sutures and modified patch shapes may reduce recurrence risk. Post-operative chest X-rays can assess surgery accuracy. A flat-appearing diaphragm might suggest a tense repair and higher recurrence risk. However, studies haven't confirmed a link between X-ray appearance and recurrence. Minimally invasive surgery is growing in paediatric surgery. CDH repair remains challenging laparoscopically and thoracoscopically. MIS benefits include less pain and fewer complications. TR isn't usually contraindicated in newborns due to tolerated hypercapnia. Thoracoscopic repair has a higher recurrence risk than open repair. Cioci et al. found more recurrence with MIS than open repair. Other studies haven't shown significant differences, though. Recent studies suggest similar recurrence risks between TR and OR in select patients.

Surgeon experience affects recurrence rates after tracheoesophageal repair (TR). More experienced surgeons have lower recurrence rates. Some studies suggest TR should be done by experienced surgeons in high-volume centres. This is because minimally invasive surgery (MIS) recurrence may be due to surgeon inexperience. Other factors may also increase recurrence risk with MIS. MIS should be limited to small defects, types A or B, as classified by the CDHSG. Other selection criteria include cardiovascular stability, no pulmonary hypertension, mild or no symptoms, liver position, late or postnatal diagnosis, and no severe health issues. More studies with long-term follow-up are needed. The time to surgery does not seem to affect recurrence risk. The link between ECMO support and recurrence needs more study. ECMO support may raise recurrence risk or signal a more severe case with a larger defect. Recurrence is not linked to repair timing (before, during, or after ECMO) or "EXIT to ECMO". These results may be skewed by a lack of standard long-term follow-up in some studies. A recent study looked at the impact of hospital volume on congenital diaphragmatic hernia (CDH) recurrence. Low-volume CDH centres have higher recurrence rates and costs than high-volume centres. Centralising CDH patients would prevent problems. Centralising CDH delivery using a hub and spoke model can improve care. It can also lower costs, complications, illness, and death [231].

12.6 Management of Recurrence

Management depends on how severe the condition is. A minor recurrence is a small defect in a patient with no symptoms. Only the omentum herniates into the chest, and it does not worsen. A major recurrence involves the stomach or bowel loops re-herniating into the chest, or worsening over time[232-234]. For minor recurrences, conservative management is a good choice. Re-operation can be avoided if the patient stays stable. Regular chest X-rays and check-ups are needed for at least five years[229].Surgery is needed when a major recurrence is found. Sutures may tear through the ribs or pull out, leading to small extra defects in Bochdalek hernia. A fault at the hiatus may be seen in other patients. An extra patch can be added without replacing the entire patch in both cases. Thoracotomy could be a good option if the recurrence is more ventral. Adhesions could affect the thoracic cavity.

There is no clear best surgical approach for CDH recurrence. Some suggest using a "virgin plane". This means using the opposite body cavity from the first surgery. The surgical field may be more accessible, with fewer adhesions and better visibility. However,

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
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a recent survey shows that recurrence is often repaired with the same technique as the first operation (laparotomy, thoracotomy, MIS) in almost half the cases. Centralising CDH care using a hub and spoke model is essential. This approach aims to improve care, lower costs, and reduce complications [231]. Management depends on how severe the condition is. A minor recurrence involves a small defect. The patient is asymptomatic, with minimal abdominal content in the thorax. Often, only the omentum is affected, and it does not worsen. A major recurrence allows stomach or bowel loops to re-enter the thorax. It may also worsen over time [214].For minor recurrences, conservative management is suitable. Re-operation is avoided if the patient remains stable. Regular chest X-rays and check-ups are needed for five years [229].

Surgery is needed for major recurrences . Sutures may tear through ribs in Bochdalek hernias. This leads to small, additional defects. A fault at the hiatus may occur in other patients. An extra patch can be added without replacing the original. Thoracotomy can be used if the recurrence is more ventral. Adhesions can affect the thoracic cavity. There is no firm agreement on the best surgical approach. Some suggest using a "virgin plane" [234]. This means operating from the opposite body cavity. It offers better visibility and fewer adhesions. A recent survey found 48% of recurrences are repaired with the same method [225]. Laparotomy is favoured over thoracotomy for open surgery. Thoracoscopy is preferred by MIS surgeons for both initial surgery and recurrence. This excludes cases of initial thoracotomy. Future studies can help determine the optimal approach. Use the most comfortable method for the surgeon when there is no clear evidence.

12.7 Second Recurrence

Second recurrences after the first repair are not well documented. The rate seems high, especially in D-defects. One study reported a 25% second recurrence rate [235]. Another series showed a 50% rate in patients with patch repairs [236]. Another study found a 19% rate, with re-repair using either patch or sutures [224]. Due to the risk of more recurrences, long-term follow-up is vital. Early detection of problems is essential. Re-re-operations are complex, so a careful technique is needed. Add a second patch over the old one to reduce harm.

12.8 Symptoms of Recurrence and Follow-Up

Symptoms of CDH recurrence include trouble swallowing and constipation. Abdominal pain, failure to thrive, and breathing issues may also occur. Assess gastrointestinal symptoms to rule out reflux or hiatal hernia. Bowel obstruction can be a sign of unrecognised hernia recurrence. However, many patients, up to two-thirds, show no symptoms when CDH is found[214]. Diagnosis is very hard without regular check-ups. CDH often comes back, and symptoms are subtle. Multidisciplinary care and follow-up are key. Tailored follow-up plans are best, based on each patient's risk. But, routine imaging for all may not be needed. This avoids unnecessary radiation for low-risk patients[228]. Recurrence can happen any time after the first fix. So, remote follow-up is useful. A team of experts should be involved. This includes neonatologists, pediatricians, and surgeons. Check-ups are advised at 3, 6, 12, 18, and 24 months[224]. After that, annual checks until age 8 are good. Clinical and X-ray tests should be standard, even with no symptoms[214]. Chest X-rays are done at 12 and 24 months. They should also be done as needed for any symptoms. After primary closure, X-rays are planned every two years until age 8. Patch repair patients need an extra X-ray at 18 months. Tests like upper GI contrast, barium enema, and CT scans are best for finding recurrence[237].

II. Conclusion

CDH remains a complex and serious problem. It can cause much illness and death. Work continues to better understand CDH. This includes causes, diagnosis, and treatments. Genomics and other studies help find the molecular basis of CDH. These offer ways to improve diagnosis and treatment. Metabolic and genomic profiles show promise as easy biomarkers. They can help with early diagnosis and prediction. More research is vital to confirm these markers. We need standard rules for their use. Prenatal treatments may help improve lung growth. This can lead to better outcomes. However, these treatments need careful patient selection. Long-term care of CDH patients is still hard. It needs good teamwork among different specialists' research and care have come a long way. But, this complex problem needs a broad approach. This includes advances in many areas. These areas include molecular biology, prenatal care, and follow-up. New tools and treatments are promising. They offer hope for better results and quality of life. Ongoing research and teamwork are key to address all parts of CDH. Cooperation between centres will help testing new advances.

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

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