

Congenital diaphragmatic hernia: a comprehensive review of pathogenesis, genetics, clinical features, and risk stratification

Hernia diafragmática congénita: revisión integral de la patogenia, la genética, las características clínicas y la estratificación del riesgo

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Abstract

Congenital diaphragmatic hernia (CDH) is a rare and complex developmental disorder characterized by diaphragmatic defects, pulmonary hypoplasia, and persistent pulmonary hypertension, leading to significant neonatal morbidity and mortality. This review summarizes current knowledge on the pathogenesis, genetic background, clinical features, and risk stratification of CDH. The etiology is multifactorial, involving genetic mutations, chromosomal abnormalities, and environmental influences, with key molecular pathways including the retinoic acid and Sonic Hedgehog signaling pathways. Advances in pre-natal diagnosis, particularly the ultrasound-based lung-to-head ratio and magnetic resonance imaging-derived total fetal lung volume, have improved prognostic assessment. Post-natal risk stratification using clinical parameters and scoring systems further guides management and predicts outcomes. Despite improvements in neonatal intensive care and surgical techniques, long-term morbidity remains a major concern. A comprehensive understanding of CDH pathophysiology and the integration of pre-natal and post-natal risk assessment are essential for optimizing individualized management strategies and improving survival and long-term outcomes.

Keywords: Congenital diaphragmatic hernia. Pulmonary hypoplasia. Pulmonary hypertension. Pathogenesis. Risk stratification.

Resumen

La hernia diafragmática congénita (HDC) es un trastorno del desarrollo raro y complejo, caracterizado por defectos diafragmáticos, hipoplasia pulmonar e hipertensión pulmonar persistente, lo que conlleva una morbilidad y una mortalidad neonatal significativa. Esta revisión resume el conocimiento actual sobre la patogenia, el trasfondo genético, las características clínicas y la estratificación del riesgo de la HDC. La etiología es multifactorial e involucra mutaciones genéticas, anomalías cromosómicas e influencias ambientales, con vías moleculares clave que incluyen el ácido retinoico y la señalización de Sonic Hedgehog. Los avances en el diagnóstico prenatal, en particular la relación pulmón-cabeza basada en ecografía y el volumen pulmonar fetal total derivado de la resonancia magnética, han mejorado la evaluación pronóstica. La estratificación del riesgo posnatal mediante parámetros clínicos y sistemas de puntuación orienta aún más el manejo y predice los resultados. A pesar de las mejoras en los cuidados intensivos neonatales y las técnicas quirúrgicas, la morbilidad a largo plazo sigue siendo una preocupación importante. Una comprensión integral de la fisiopatología de la HDC y la integración de la evaluación de los riesgos

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Date of reception: 30-04-2026

Date of acceptance: 14-06-2026

DOI: 10.24875/CIRU.26000144

Cir Cir. (ahead of print)

Contents available at PubMed

www.cirugiaycirujanos.com

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prenatal y posnatal son esenciales para optimizar las estrategias de manejo individualizadas y mejorar la supervivencia y los resultados a largo plazo.

Palabras clave: *Hernia diafragmática congénita. Hipoplasia pulmonar. Hipertensión pulmonar. Patogenia. Estratificación del riesgo.*

Introduction

Congenital diaphragmatic hernia (CDH) is a rare developmental anomaly characterized by incomplete development of the diaphragm, allowing abdominal organs to herniate into the thoracic cavity and impair lung development. Depending on the anatomical location of the diaphragmatic defect, it is referred to by different names. A posterolateral defect of the diaphragm is called a Bochdalek hernia, whereas an anterior defect is termed a Morgagni hernia. There are also diaphragmatic hernias in which the diaphragm is intact, such as a hiatal hernia and diaphragmatic eventration.¹⁻³ The most common and clinically the most severe form is Bochdalek hernia, and this is the type primarily known as CDH.^{1,2}

In CDH, increased intrathoracic pressure leads to major cardiopulmonary abnormalities. Pulmonary hypoplasia impairs lung development and gas exchange, while associated vascular remodeling contributes to pulmonary hypertension. These changes may also affect cardiac development, particularly the left ventricle.^{1,4-6}

Management of CDH requires intensive and multidisciplinary neonatal intensive care. Advanced cardiopulmonary resuscitation is often necessary. Although the diaphragmatic defect can be successfully repaired, a significant proportion of patients develop multisystem morbidity.⁷ In addition, standard intensive care management is insufficient for approximately 30% of infants with CDH, and these patients may be treated with extracorporeal life support (extracorporeal membrane oxygenation [ECMO]).^{6,8}

In recent years, the survival rates of CDH patients have improved. With gradually increasing survival, the long-term prognosis and quality of life of these patients have become increasingly important. It has been shown that survivors are at risk for many long-term morbidities, emphasizing the importance of long-term follow-up care for these children. The purpose of this review is to provide an overview of current knowledge regarding CDH.

Epidemiology and prevalence

The global prevalence of CDH is approximately 2.3/10,000 live births.⁹ However, due to the limited

number of population-based studies, the true rate remains uncertain. Most data originate from regions in North America and Europe.⁹

CDH does not show a consistent trend regarding sex, although some studies report a slight male predominance.^{9,10} However, in a study by Sferra et al., it was emphasized that mortality was higher among females diagnosed with CDH.¹¹

The prevalence rates between isolated CDH and non-isolated CDH (patients with associated cardiac or chromosomal anomalies) remain unclear.¹ Nevertheless, the frequency of coexistence with congenital heart defects is approximately 15%.^{10,12} and these include major malformations (Tetralogy of Fallot, atrioventricular septal/canal defects, pulmonary valve defects, transposition of the great arteries, truncus arteriosus, total anomalous pulmonary venous return, and hypoplastic ventricular anomalies), minor cardiac malformations (including atrial septal defect and ventricular septal defect), and aortic anomalies. Other major structural anomalies include renal anomalies in 5%,¹⁰ limb anomalies in 5%,¹⁰ central nervous system anomalies in 5%,¹⁰ bronchopulmonary sequestration in 3.4%,¹³ and omphalocele in 0.6%.¹⁴

A meta-analysis conducted by Montalva et al. investigated the link between CDH and adverse pregnancy outcomes. Their findings indicated a significant prevalence of the condition, occurring in 28% of stillbirths and 27% of pregnancy terminations (Fig. 1).¹²

Embryology and pathogenesis

The diaphragm is a vital skeletal muscle that separates the thoracic and abdominal cavities and plays a primary role in respiration. It develops during the 8th week of intrauterine life through the fusion of four structures: the septum transversum (tendon component), the pleuroperitoneal folds (PPFs) (muscle component), the thoracic wall mesenchyme, and the esophageal mesentery (crura of the diaphragm).^{1,15,16}

The structures specific to the developing diaphragm are the PPFs. These are two temporary pyramid-shaped structures located between the thoracic (pleural) and abdominal (peritoneal) cavities, which expand

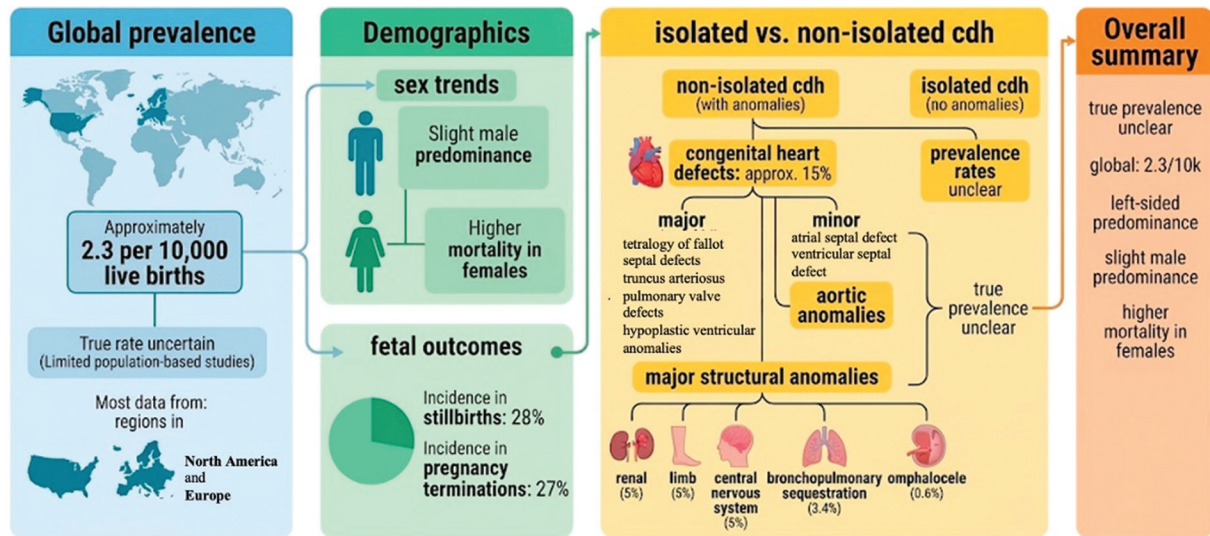


Figure 1. Global epidemiology, prevalence, and clinical characteristics of congenital diaphragmatic hernia.

dorsally and ventrally along the septum transversum, a thin membrane on the cranial surface of the liver, and form the connective tissue and central tendon of the diaphragm.¹⁵⁻¹⁸ Typically, closure occurs earlier on the right side than on the left, which explains the higher frequency of left-sided CDH.¹⁸ The axons of the phrenic nerve originate from the C3-C5 segments of the neural tube and extend into the PPFs in a manner similar to muscle precursor cells. The diaphragm's final major component is its vascular system, although its embryonic origin remains unknown.¹⁵ The PPFs and muscle connective tissue are critical for diaphragm development, and mutations in PPF-derived fibroblasts represent a source of CDH.¹⁶

The etiology of CDH is multifactorial. Maternal risk factors include age, pre-gestational diabetes, pre-gestational hypertension, low maternal body mass index, tobacco use, and alcohol consumption.^{1,19} Exposure to fine particulate matter (PM2.5) during pregnancy is thought to affect fetal development through oxidative stress, inflammation, and placental dysfunction. Although associations between PM2.5 and various congenital anomalies have been reported, studies specifically evaluating its relationship with CDH are limited. Current evidence indicates that there are insufficient data to establish a definitive role for air pollution in CDH etiology, and larger, targeted studies are needed to clarify this association.²⁰ In addition, some studies have demonstrated a significantly increased risk of CDH associated with maternal use of hairspray in the pre-pregnancy period.²¹

The common pathological features observed in all CDH cases are best characterized by significantly reduced airway branching and alveolar surface area, decreased pulmonary vascularization, hypertrophy of pulmonary arterial smooth muscle, abnormal vascular smooth muscle development with aberrant reactivity, and cardiac hypoplasia primarily affecting the left ventricle.^{1,5,22} These changes occur not only in the ipsilateral lung but also in the contralateral lung. There is variability in the lung phenotype of patients with CDH, particularly in the degree of vascular remodeling, and this variability reflects differences in clinical severity.^{1,23}

Genetic factors also play an important role in the pathogenesis of CDH. Although most cases are sporadic, genetic mutations and chromosomal abnormalities (e.g., trisomies 18, 13) are associated with a subset of patients. Specific genes involved in diaphragm development, such as GATA4, ZFPM2, and FOG2, have been proposed to contribute to the pathogenesis of CDH, particularly in syndromic forms.^{24,25}

Genetics and molecular mechanisms

CDH exhibits significant phenotypic variability and has a complex etiology involving both genetic and environmental factors. The genetic spectrum of CDH includes chromosomal abnormalities, copy number variants (CNVs), monogenic syndromes, and multifactorial inheritance patterns. Despite advances in genomic technologies, the molecular mechanisms underlying CDH have not yet been fully elucidated, highlighting the need

for more detailed investigation of genetic contributions to the pathogenesis of the disease.²⁶⁻²⁸

CDH subtypes and their genetic correlations

CDH subtypes are primarily classified according to defect size, anatomical location, and associated anomalies. Bochdalek hernias, the most common subtype, are typically left-sided. Pre-natal predictors of survival include defect size, presence of associated malformations, lung volume, liver herniation, and lung-to-head ratio (LHR). Larger defects are associated with higher mortality and a greater burden of anatomical malformations, suggesting the presence of broad genetic abnormalities such as large chromosomal deletions (e.g., 15q26, 17q12) that may affect multiple genes critical for diaphragm development and embryogenesis. In contrast, single-nucleotide variants in genes such as FBN1 or TGFB3 are associated with smaller defects. In addition, isolated CDH and complex CDH (with additional anomalies) differ genetically; complex cases frequently harbor *de novo* pathogenic variants and are associated with a poorer prognosis.^{26,27}

Chromosomal abnormalities and CNVs

Chromosomal aneuploidies, large deletions/duplications, and complex rearrangements detectable by karyotyping or microarray analysis account for 10-35% of cases, particularly in non-isolated CDH.²⁸ The most common aneuploidy associated with CDH is trisomy 18, followed by trisomies 13, 9, 16, and sex chromosome abnormalities such as Turner syndrome (45,X) and trisomy X (46,XXX).^{28,29} These cytogenetic abnormalities are associated with increased neonatal mortality.

CNVs are emerging as major contributors to CDH pathogenesis. Frequently recurrent CNV regions include deletions at 8p23.1, 15q26.1, 1q41-42, and 8q23.1; candidate genes in these regions, such as GATA4, SOX7, COUP-TFII, DISP1, HLX, and ZFPM2/FOG2, play critical roles in diaphragmatic and cardiac development.^{27,30,31} For example, GATA4 is a key transcription factor for heart and diaphragm morphogenesis and is regulated by retinoid signaling pathways, which are also implicated in CDH pathogenesis.³²⁻³⁴ ZFPM2/FOG2 functions as a transcriptional corepressor in retinoid pathways, and mutations in this gene may cause isolated or syndromic CDH.^{24,35,36} Pallister-Killian syndrome, caused by mosaic tetrasomy 12p, is a

classic CNV syndrome with up to 50% prevalence of CDH, illustrating the role of chromosomal mosaicism in disease expression.^{29,37,38}

Single-gene mutations and syndromic associations

More than 20 genes have been identified in syndromic and non-syndromic CDH cases.²⁸ Autosomal recessive syndromes such as Donnai-Barrow syndrome (LRP2 mutations) and Matthew-Wood syndrome (STRA6, RARB mutations) involve diaphragm defects accompanied by multisystem anomalies.^{28,29}

The *LRP2* gene encodes megalin, a multiligand receptor involved in endocytosis, which may participate in the transport and signaling of Sonic Hedgehog and retinoid precursors during embryogenesis.³⁹ Genes involved in retinoic acid signaling, such as STRA6 and RARB, also play critical roles in diaphragm development and CDH pathogenesis.⁴⁰ These findings highlight the importance of an interconnected molecular network involving Sonic Hedgehog and retinoid pathways in CDH etiology.

Among autosomal dominant disorders, WT1-related conditions (such as Denys-Drash syndrome) present with combined genitourinary and diaphragmatic anomalies linked to disruption of retinoic acid-mediated pathways. CDH may also rarely occur in connective tissue disorders such as Cornelia de Lange syndrome (NIPBL mutations) and Marfan syndrome (FBN1 mutations), reflecting genetic pleiotropy and the ability of single genes to produce multiple phenotypic outcomes.^{41,42} X-linked syndromes, including craniofrontonasal syndrome (EFNB1 mutations) and Simpson-Golabi-Behmel syndrome (GPC3 mutations), further expand the genetic heterogeneity of CDH. The genetic basis of classic CDH-associated syndromes such as Fryns syndrome and thoracoabdominal syndromes remains incompletely understood, suggesting underlying genetic heterogeneity and possible polygenic inheritance.²⁸

Molecular pathways and functional insights

Multiple molecular pathways play essential roles in CDH pathogenesis. Retinoic acid signaling is fundamental for diaphragm development; defects or mutations in this pathway (e.g., STRA6, RARB, and COUP-TFII) disrupt normal morphogenesis. Similarly,

alterations in TGF- β /SMAD signaling have been demonstrated in the lungs of CDH patients and shown to be associated with pulmonary hypertension and lung hypoplasia.⁴³ MicroRNA regulation (such as increased miR-200b) modulates these pathways and influences disease severity in animal models. Mutations in transcription factors such as GATA4, SOX7, ZFPM2/FOG2, and HLX disrupt gene networks involved in tissue differentiation and organogenesis. The Sonic Hedgehog pathway also has a role in diaphragm and adjacent organ development through LRP2.⁴⁴

The genetic complexity of CDH is further amplified by factors such as variable expressivity, incomplete penetrance, locus heterogeneity, and polygenic influences, making genetic diagnosis and counseling challenging. Somatic mosaicism, although difficult to detect, may underlie some cases. New-generation sequencing techniques such as whole-exome sequencing facilitate the identification of *de novo* mutations and rare variants, improving understanding of genetic contributions and enabling individualized genetic counseling.²⁶⁻²⁸

Multifactorial etiology and environmental interactions

Although numerous genetic factors have been identified, a specific genetic cause cannot be determined in approximately 80% of CDH cases, suggesting a multifactorial etiology. Epidemiological studies have associated maternal obesity, hypertension, certain medications, and particularly Vitamin A/retinoid deficiency with increased CDH risk.^{33,45} Epigenetic modifications and gene-environment interactions modulate gene expression during diaphragm development. Significant clinical differences in CDH phenotype have been observed among monozygotic twins, despite identical genetic backgrounds, suggesting that environmental and epigenetic factors influence phenotypic variability.⁴⁶ In addition, markedly reduced retinol and retinol-binding protein levels in cord blood of newborns with CDH indicate that disruptions in retinoid metabolism may contribute to CDH pathogenesis.⁴⁷

Clinical implications and genetic counseling

Detailed phenotyping, family history evaluation, chromosomal microarray analysis, and targeted or exome

sequencing are essential for assessing prognosis, guiding clinical management, and estimating recurrence risk in CDH. Identification of a genetic etiology assists in pre-natal decision-making and may guide interventions such as preimplantation genetic testing. Although many cases cannot be genetically explained, negative genetic results are generally reassuring in the absence of a family history.²⁵ As genetic knowledge advances, personalized therapeutic approaches and improved clinical outcomes for CDH patients are likely to become increasingly achievable.²⁸

Pulmonary and cardiovascular pathophysiology

Under normal circumstances, lung development progresses through the pseudoglandular and canalicular phases between the 14th and 16th weeks of intrauterine life, during which airway branching and the vascular network are established. In the presence of CDH, herniation of abdominal organs into the thoracic cavity and mechanical compression disrupt the morphogenesis of lung parenchyma and vascular structures during these critical developmental stages, resulting in pulmonary hypoplasia. In hypoplastic lungs, the number of bronchial branches is reduced, the number of alveolar units is insufficient, and epithelial maturation is delayed; these morphological characteristics limit gas exchange. In addition, decreased numbers of type II pneumocytes and inadequate surfactant production have been observed in hypoplastic lung tissue, contributing to worsened post-natal respiratory function. Moreover, the pulmonary vascular structures also develop abnormally in CDH patients; increased hypertrophy and remodeling of distal pulmonary arterioles are associated with elevated pulmonary vascular resistance and persistent pulmonary hypertension of the newborn. These pathophysiological processes frequently affect the ipsilateral lung, but alterations may also be observed in the contralateral lung, supporting systemic effects on lung development and the “dual-hit hypothesis.”⁴⁸⁻⁵⁰

The dual-hit hypothesis has been proposed to explain the morphological and functional impairment of lung development. According to this model, lung hypoplasia in fetuses with CDH occurs through a two-stage process:

- First hit (primary effect): a fundamental defect in lung development caused by genetic and/or early embryologic factors. At this stage, the basic morphogenesis of the diaphragm and lung

is impaired, and the initial lung volume and alveolar potential are limited.

- Second hit (secondary effect): mechanical compression and increased intrathoracic pressure resulting from herniation of abdominal organs into the thoracic cavity due to the diaphragmatic defect. This mechanical pressure further restricts ipsilateral lung growth and alveolar/bronchial branching and contributes to pulmonary vascular remodeling and hypertension.

Some evidence suggests that the contralateral lung is also indirectly affected. This supports the view that the CDH phenotype results not only from the diaphragmatic defect but also from early embryologic lung developmental abnormalities combined with mechanical compression. This concept helps explain both phenotypic heterogeneity in CDH and bilateral lung involvement. Teratogenic animal models further support this hypothesis by showing lung hypoplasia before the diaphragmatic defect is fully formed, suggesting a primary developmental origin.⁵⁰⁻⁵²

The hallmark of CDH pathophysiology is the combination of pulmonary hypoplasia and persistent pulmonary hypertension. Hypoplastic lungs exhibit reduced airway branching, decreased surfactant levels, and reduced alveolar surface area, all of which impair gas exchange. Simultaneously, hypertrophy of distal pulmonary arterioles increases pulmonary vascular resistance, contributing to neonatal pulmonary hypertension. Right-to-left shunting through fetal circulatory pathways leads to systemic hypoxemia and complicates neonatal management.^{49,50}

Associated cardiac anomalies further exacerbate hemodynamic instability. Cardiovascular malformations range from simple septal defects to complex outflow tract anomalies and great vessel abnormalities. Although left heart hypoplasia has been described, its contribution to clinical severity is not fully understood. The interaction between pulmonary vascular disease and congenital heart defects complicates hemodynamic management and significantly influences patient prognosis.^{49,50,52,53}

Clinical features

CDH can often be identified prenatally through obstetric ultrasonography by detecting the herniation of intra-abdominal organs into the thoracic cavity. In more severe cases, polyhydramnios may appear as an additional prenatal finding. In the post-natal period, affected newborns typically present with marked respiratory distress,

inadequate oxygenation, a scaphoid (sunken) abdomen, thoracic asymmetry, and displacement of heart sounds to the contralateral side. Breath sounds on the side of the herniation are diminished or completely absent. In severe cases, low Apgar scores at 1 and 5 min are observed. Without appropriate and timely initiation of respiratory support, the clinical condition deteriorates rapidly, and the mortality risk increases significantly.^{49,54,55}

Respiratory symptoms largely arise from impaired gas exchange due to pulmonary hypoplasia and persistent pulmonary hypertension. Pulmonary hypertension results from arteriolar constriction and involvement of the pulmonary arterial bed; this necessitates the persistence of the fetal circulatory pattern, in which blood from the right ventricle is diverted away from the lungs and toward the systemic circulation, thereby preventing effective gas exchange. In some cases, this pulmonary hypertension develops a few hours after birth as the transitional circulation adapts to post-natal life. Hypoxia, acidosis, stress, or other factors may abruptly end this “honeymoon” period and re-establish fetal shunting.^{49,56}

Interestingly, not all CDH cases present immediately after birth. Some patients manifest mild respiratory difficulty later in infancy or childhood, or the condition may be detected incidentally. In such cases, a hernia sac containing displaced organs is more commonly present, which may mitigate symptom severity.^{49,57}

Long-term morbidity is common among CDH survivors. Chronic lung disease initially appears as restrictive defects due to hypoplasia, followed by airway obstruction related to reactive airway disease. Lung function may improve during childhood but can deteriorate in adulthood. Persistent pulmonary hypertension, gastrointestinal complications, developmental delays, neurological deficits, hearing loss, and musculoskeletal abnormalities are additional concerns.⁵²

Quality-of-life assessments show that CDH survivors often experience reduced physical functioning and diminished psychosocial well-being. These findings highlight the need for multidisciplinary follow-up to enable early detection and management of emerging complications and improve overall outcomes.⁵²

Pre-natal diagnosis

Various methods are used to determine disease severity in CDH, identify associated structural and/or genetic abnormalities, and predict outcomes through risk

stratification. Particularly in recent years, advances in pre-natal imaging and genetic testing have shifted the pre-natal diagnosis and management of CDH, enabling earlier detection, improved risk classification, and optimized perinatal care.⁵⁸

At least two-thirds of CDH cases are detected pre-natally, most commonly by pre-natal ultrasonography at around 24 weeks of gestation.^{1,59,60} After diagnosis, prognosis and delivery planning depend on detailed fetal ultrasonography, magnetic resonance imaging (MRI), and echocardiographic findings.⁵⁸ Pre-natal genetic testing is recommended to exclude an underlying chromosomal abnormality, and for this purpose, amniocentesis is typically performed in the second trimester.⁶¹

The gestational age at diagnosis is associated with prognosis.⁶² Numerous studies have demonstrated that CDH diagnosed before 25 weeks of gestation is associated with increased morbidity, including higher mortality rates, more severe respiratory symptoms, and a greater likelihood of requiring patch repair.⁶³ Mortality rates differ significantly depending on the trimester in which the diagnosis is made, with first-trimester detection associated with the poorest prognosis.⁶³

The key ultrasonographic finding is visualization of intra-abdominal organs within the thoracic cavity and the inability to assess diaphragmatic continuity. Left-sided CDH is the most common form and is typically characterized by herniation of the stomach, bowel loops, and, in some cases, the liver into the thorax. This often results in mediastinal deviation, with displacement of the heart and great vessels toward the right hemithorax. The stomach can be easily identified ultrasonographically due to its fluid content, whereas bowel loops can be distinguished by observing peristaltic movements.⁶⁴ In contrast, the liver poses a diagnostic challenge because its echogenicity closely resembles that of lung parenchyma.⁶⁰ Right-sided CDH accounts for approximately 15% of cases and is more difficult to detect prenatally. This is primarily because the stomach generally remains in an abdominal position, and herniated liver tissue has echogenic characteristics similar to lung parenchyma on ultrasonography. Consequently, pre-natal detection rates for right-sided hernias are reported to be lower.^{62,65} Doppler ultrasonography, evaluating the positions of the umbilical vein, hepatic vessels, and gallbladder, can assist in determining liver localization.⁶³ However, indirect ultrasonographic findings such as cardiac compression, mediastinal deviation,

and polyhydramnios may support the diagnosis but are insufficiently specific when considered alone.⁶⁶

The most common conditions in the differential diagnosis include congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration, and congenital lobar emphysema.^{60,64} CPAM is typically characterized by a cystic or solid intrathoracic mass with an intact diaphragm; peristalsis is not observed within the lesion. In bronchopulmonary sequestration, abnormal lung tissue receives a systemic blood supply, and detection of an aberrant feeding artery originating from the aorta on Doppler ultrasonography is diagnostic. Congenital lobar emphysema is characterized by overinflation of a lung lobe and generally becomes more apparent in the post-natal period. In addition, mediastinal cysts or teratomas, enteric duplication cysts, and thymic cysts should also be considered in the differential diagnosis.

Risk stratification

Risk stratification in CDH is highly valuable for patient management. Prenatally, it guides counseling, selection of an appropriate delivery center, and planning of fetal therapy options. Postnatally, it reflects the physiological condition of the newborn and directs intensive care management. In this context, risk stratification plays a critical role in predicting ECMO requirements, monitoring treatment response, and determining prognosis. The combined use of pre-natal and post-natal risk stratification enables a more accurate assessment of disease severity and the development of individualized management strategies.

Pre-natal risk stratification

In fetuses with CDH, pre-natal imaging parameters remain the most reliable tools for predicting neonatal mortality and morbidity. Two major parameters are primarily used: the LHR, obtained by ultrasound, and the total fetal lung volume (TFLV), measured by MRI.

The LHR is calculated by measuring the cross-sectional area of the fetal lung on the side opposite the herniation at the level of the four-chamber cardiac view and dividing it by the fetal head circumference.⁶⁷ However, the use of anteroposterior diameter, longest axis, or planimetric tracing methods introduces variability and reproducibility challenges. To reduce these limitations, the observed-to-expected LHR (o/e-LHR), adjusted for gestational age, has become more widely

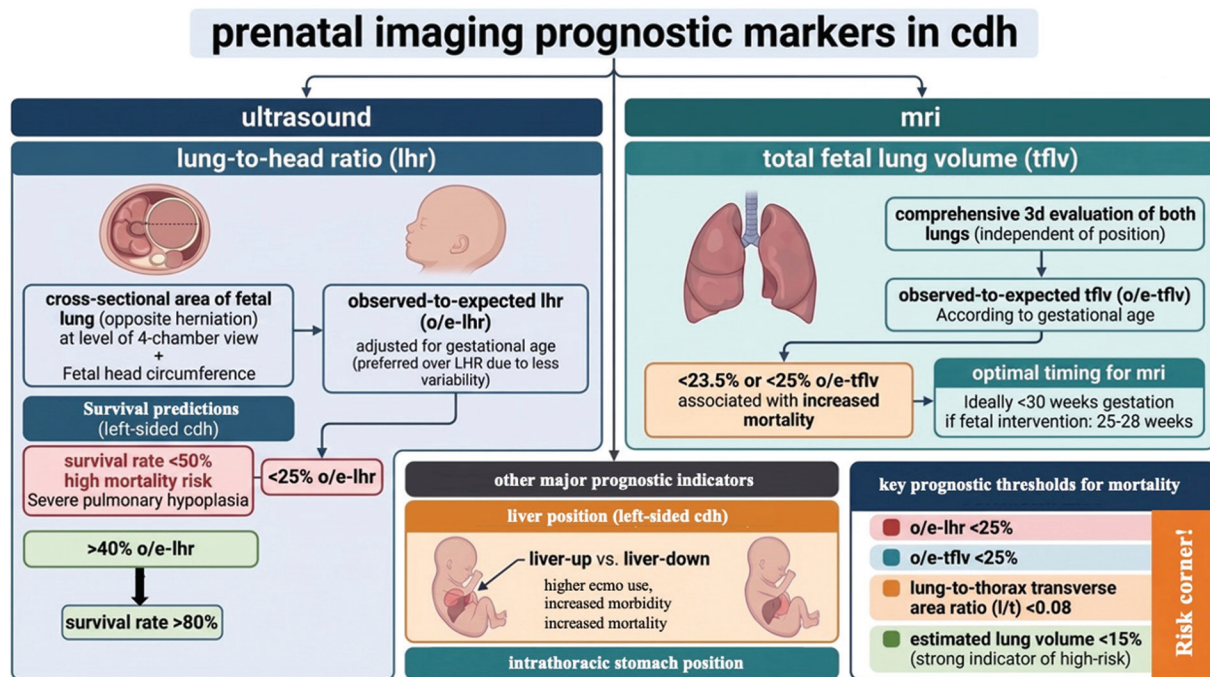


Figure 2. Pre-natal imaging markers for risk stratification in congenital diaphragmatic hernia.

used.⁶⁸ Major limitations of LHR measurement include the inability to reliably assess the ipsilateral lung, the risk of inadvertently including adjacent structures (e.g., the spleen), and the fact that the assessment relies on a single cross-sectional plane. Nevertheless, an LHR below 1 or an o/e-LHR below 25% is strongly associated with increased mortality risk and severe pulmonary hypoplasia.^{62,68-70} In left-sided CDH, an o/e-LHR < 25% predicts a survival rate below 50%, whereas an o/e-LHR > 40% predicts a survival rate above 80%.^{1,71}

MRI-derived measurement of TFLV is more comprehensive, allowing three-dimensional evaluation of both lungs independently of fetal position or maternal body habitus.^{62,63} MRI can additionally be used to calculate the observed-to-expected TFLV (o/e-TFLV) ratio according to gestational age.⁶³ In a study by Tanacan et al. evaluating CDH cases, o/e-LHR ≤ 22.5% and o/e-TFLV ≤ 23.5% were identified as significant predictors of neonatal mortality.⁷² The optimal timing for MRI in pre-natal risk assessment of CDH is generally before 30 weeks of gestation, and if fetal intervention is being considered, the ideal timing is between 25 and 28 weeks.^{62,73,74}

In left-sided CDH, the position of the liver is among the most important prognostic indicators. The presence of liver above the diaphragm (termed “liver-up”)

has long been associated with higher ECMO utilization, increased morbidity, and increased mortality.^{1,60,62,75} Other prognostic markers affecting survival include intrathoracic stomach position and the lung-to-thorax transverse area ratio (L/T). However, their clinical use remains limited due to a lack of standardization, variable measurement techniques, and lower prognostic accuracy compared with more widely accepted parameters such as LHR and o/e-LHR.^{1,70,76} Another parameter used by some centers is lung volume assessment. An estimated lung volume below 15% has been shown to be a strong indicator of high-risk CDH.⁷⁷ Recent systematic reviews have demonstrated that an o/e-LHR < 25%, o/e-TFLV < 25%, and a lung-to-thorax transverse area ratio (L/T ratio) < 0.08 are strongly associated with increased neonatal mortality (Fig. 2).^{76,78}

Post-natal risk stratification

In the early post-natal period, particularly within the first 24 h, several parameters significantly influence prognosis. These include blood gas abnormalities, APGAR scores, and the oxygenation index (OI). In the early period, a partial CO₂ (PCO₂) level > 60 mmHg on blood gas analysis is associated with increased ECMO use and lower survival rates.⁷⁹ The OI is an

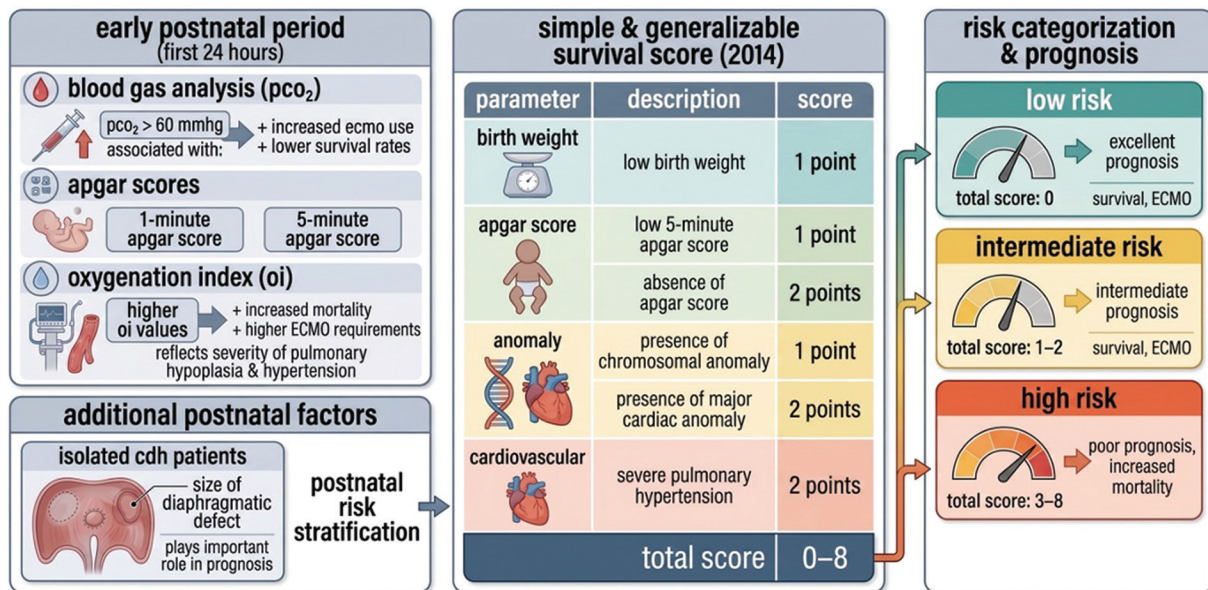


Figure 3. Post-natal risk stratification in congenital diaphragmatic hernia.

important indicator reflecting the severity of pulmonary hypoplasia and pulmonary hypertension in the post-natal period. It is used to evaluate oxygenation status in mechanically ventilated newborns, and higher OI values are associated with increased mortality and higher ECMO requirements.⁸⁰ In isolated CDH patients, the size of the diaphragmatic defect also plays an important role in prognosis and has been included in post-natal risk stratification in some studies.⁸¹ In 2014, a simple and generalizable survival score, easily calculated at the bedside, was developed. This score includes five parameters: low birth weight (1 point), low 5-min Apgar score (1 point), absence of Apgar score (2 points), presence of chromosomal anomaly (1 point), presence of major cardiac anomaly (2 points), and severe pulmonary hypertension (2 points). A total score of 0 indicates low risk, 1-2 indicates intermediate risk, and 3-8 indicates high risk (Fig. 3).⁸²

Conclusions

CDH is a complex and multisystemic disorder shaped by the interplay of pulmonary hypoplasia, persistent pulmonary hypertension, and various genetic-molecular mechanisms. Despite significant advancements in pre-natal imaging, genetic diagnostics, and neonatal intensive care, these core pathophysiological elements continue to dictate the severity of the disease and limit clinical outcomes. Current evidence demonstrates that

CDH is not merely a structural diaphragmatic defect, but a multifactorial disorder arising from the collective contributions of genetic, environmental, and embryological factors. Individualized and multidisciplinary management starting from the pre-natal period, alongside the development of future targeted fetal therapy strategies, will play a key role in improving both survival and quality of life.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence.

The authors declare that ChatGPT was used for language editing and figure editing.

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