Congenital lung malformations

Federica Pederiva[1] ✉, Steven S. Rothenberg[2], Nigel Hall[3], Hanneke Ijsselstijn[4], Kenneth K. Y. Wong[5], Jan von der Thüsen[6], Pierluigi Ciet[7,8], Reuven Achiron[9], Adamo Pio d'Adamo[10,11] & J. Marco Schnater[12]

Abstract

Congenital lung malformations (CLMs) are rare developmental anomalies of the lung, including congenital pulmonary airway malformations (CPAM), bronchopulmonary sequestration, congenital lobar overinflation, bronchogenic cyst and isolated congenital bronchial atresia. CLMs occur in 4 out of 10,000 live births. Postnatal presentation ranges from an asymptomatic infant to respiratory failure. CLMs are typically diagnosed with antenatal ultrasonography and confirmed by chest CT angiography in the first few months of life. Although surgical treatment is the gold standard for symptomatic CLMs, a consensus on asymptomatic cases has not been reached. Resection, either thoracoscopically or through thoracotomy, minimizes the risk of local morbidity, including recurrent infections and pneumothorax, and avoids the risk of malignancies that have been associated with CPAM, bronchopulmonary sequestration and bronchogenic cyst. However, some surgeons suggest expectant management as the incidence of adverse outcomes, including malignancy, remains unknown. In either case, a planned follow-up and a proper transition to adult care are needed. The biological mechanisms through which some CLMs may trigger malignant transformation are under investigation. *KRAS* has already been confirmed to be somatically mutated in CPAM and other genetic susceptibilities linked to tumour development have been explored. By summarizing current progress in CLM diagnosis, management and molecular understanding we hope to highlight open questions that require urgent attention.

Introduction

Congenital lung malformations (CLMs) refer to a continuum of developmental disorders that involve the lung parenchyma, the tracheobronchial tree and the pulmonary vessels, or a combination of the above. At one end of the spectrum, congenital lobar overinflation (CLO; previously known as congenital lobar emphysema) represents abnormal lung supplied by normal vessels. At the other end of the spectrum, pulmonary arteriovenous malformations are characterized by abnormal vessels within normal lung parenchyma[1].

This Primer focuses on the most common congenital lung anomalies: congenital pulmonary airway malformation (CPAM; previously known as congenital cystic adenomatoid malformation, CCAM), bronchopulmonary sequestration (BPS), CLO and bronchogenic cyst. We also discuss congenital bronchial atresia (CBA), which has been recognized as a separate CLM entity. BPS can be intralobar (ILS) or extralobar (ELS). CPAM is further classified into five histological subtypes, defined by the suspected anatomical level of the airway they originate from[2,3] (Fig. 1). Of note, some clinicians and researchers consider all the CLMs under the umbrella of CPAM but CPAM is only one of the CLM types, and adherence to the precise definition of each CLM is required when reporting new cases. CLMs arise during embryonic lung development (Box 1) as a result of abnormal organogenesis or dysregulation of cellular signalling within the epithelial–mesenchymal interaction[4]. The timing of this dysregulation is likely to determine the type or subtype of CLM.

Most newborns with CLMs are asymptomatic, and fewer than 10% have respiratory symptoms. Professionals agree to surgically treat symptomatic patients with CLMs, but there is an ongoing debate worldwide on whether asymptomatic patients should be managed surgically or conservatively. Prophylactic elective surgery is recommended in asymptomatic cases to avoid the long-term risk of development of pulmonary infections and to prevent possible malignant transformation. The best way to address this controversy is to invest resources into researching the natural history of CLMs, the biological relationship between CPAM, BPS, bronchogenic cyst and malignancy, and the potential drivers of malignant transformation. In addition, clinical professionals, surgeons and researchers continue to envision prognostic tools, standardize care (especially in asymptomatic cases), standardize respiratory and imaging follow-up, provide transition of care into adulthood, and build a global registry.

This Primer describes the epidemiology and pathophysiology of CLMs as well as progress in their diagnosis and management, and the different viewpoints of paediatric and non-paediatric thoracic surgeons on CLM management.

Epidemiology

Demographics

CLMs have been estimated to comprise up to 18% of all congenital anomalies[5]. Historically, the overall incidence of CLMs was estimated at ~0.5 to 1.5 per 10,000 live births but, in 2015, registry studies in the UK reported an incidence of ~1 per 2,500 live births[6–9]. The apparent rising incidence of these malformations is probably a consequence of the widespread availability and improved resolution of prenatal ultrasonographic screening, which have increased CLM detection, especially in high-income countries[8,10]. Due to a lack of global registries, the exact number of patients with these rare malformations and possible regional differences remains unknown.

CPAM type 1 is the most common type of CPAM, representing 50–70% of cases[11]. CPAM type 2 underlies 15–30% of all CPAM cases[12], whereas CPAM type 3 represents 5–10%[12]. The individual incidence of other CLMs remains unknown.

Around 11.7% of patients with a CLM have an associated anomaly in other organs but only 5–10% of them have an additional major malformation[13]. Associated developmental defects in other organ systems may therefore stem from the same dysregulation in epithelial–mesenchymal interactions during embryonic development that causes CLMs, but this link has not yet been demonstrated. The most common associated malformations are congenital heart defects (32%) and gastrointestinal defects (18%)[14]. Bronchogenic cysts have been found to have the highest proportion of associated anomalies (29%), particularly vascular malformations, followed by CPAM (12%), which is more frequently associated with congenital heart diseases and gastrointestinal malformations. A concurrent malformation exists in 10% of patients with BPS and in 9% of those with CLO, mainly gastrointestinal for BPS and cardiac for CLO[14]. Clinicians should be aware of these possible co-occurring anomalies and consider additional diagnostic imaging.

Risk factors

CLMs seem to occur sporadically and have not been associated with any karyotype anomalies[15]. Their formation has not been associated with maternal factors, such as race or age, or exposure to environmental factors[15]. No sex predilection has been demonstrated[15]. Risk factors for developing symptoms after birth are not yet known. Multicentre international collaborations, including long-term follow-up registries, and prospective trials, such as the CONNECT trial by the Collaborative Neonatal Network, together with the equally needed molecular biology studies[16] will help understand the natural history of CLMs and how some of them (CPAM, BPS and bronchogenic cyst) may be associated with malignant transformation.

Association of CLMs with lung cancer. The incidence of malignant degeneration in CLMs remains unknown; in 1983 (ref. 17), it was estimated to be 4% considering all CLMs. In 2010 (ref. 18), the incidence of pleuropulmonary blastoma (PPB), specifically, was found to be 2% in CPAM. PPB has been historically associated with CPAM but it remains unclear whether the initially identified lesion is a CPAM preceding PPB or an unrecognized PPB[19]. In earlier studies, CLOs in two children were associated with a PPB[20] and a rhabdomyosarcoma[21], respectively, and CLOs in ten adults, at that time diagnosed as congenital cystic emphysema, were associated with bronchogenic carcinoma[22]; however, the histological definition of these CLOs might have been inaccurate. On the other hand, it has been suggested that a CPAM type 4 evolves into PPB through the acquisition of a somatic mutation in *DICER1* (refs. 23,24). However, a specific relationship between *DICER1* mutations and CPAM or other CLMs predisposition to malignancy has not yet been demonstrated. A pathognomonic molecular marker for PPB has not yet been discovered but an association with *DICER1* heterozygous germline mutation is found in up to 66% of PPBs. Mutations in *DICER1* are known to considerably increase the risk of several types of cancer, including PPB. DICER1 syndrome predisposes to the development of tumours in the lung, kidney, ovary and thyroid[23]. To comprehensively elucidate the complex interplay between germline and somatic mutations in *DICER1* and PPB, initiatives such as the International PPB/DICER1 Registry and the DICER1-Related Pleuropulmonary Blastoma (PPB) Syndrome Study conducted by the National Cancer Institute are essential. These projects are extremely useful in characterizing the risk associated with pathogenic variants, studying the clinical course of patients with these variants, improving management and,

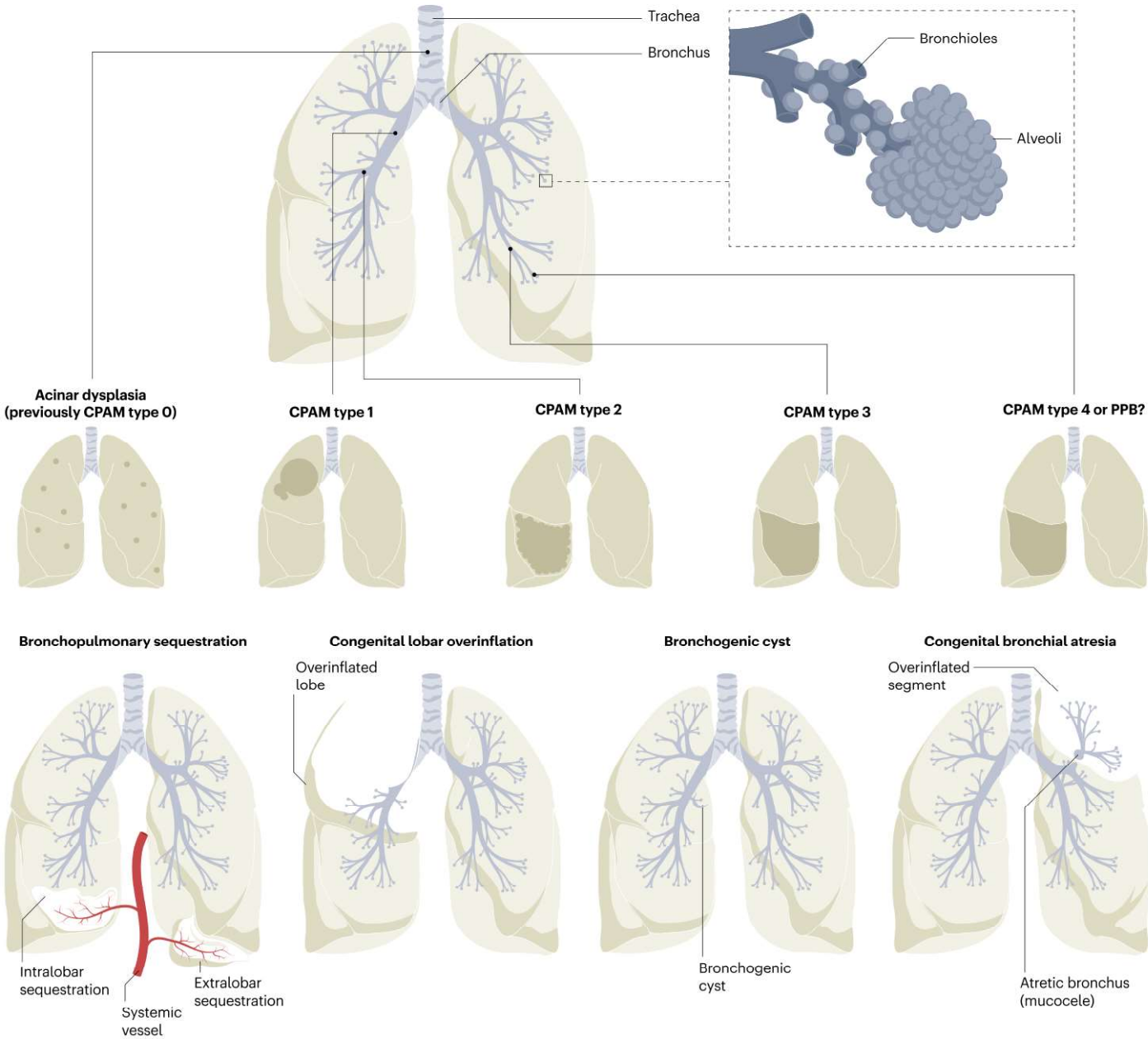


Fig. 1 | Types of CLM. Abnormal organogenesis or dysregulation of cellular signalling within the epithelial–mesenchymal interaction during embryonic development might cause a congenital lung malformation (CLM). The timing of this dysregulation determines the type of CLM, which include five subtypes of congenital pulmonary airway malformation (CPAM); bronchopulmonary sequestration, which can be intralobar or extralobar; congenital lobar overinflation; bronchogenic cyst; and congenital bronchial atresia. Stocker classification identifies five types of CPAM; however, CPAM type 0 should now be called acinar dysplasia, and CPAM type 4 is doubted to be a pleuropulmonary blastoma (PPB). CPAM type 1 arises from the proximal bronchioles or distal bronchi, CPAM type 2 from the bronchioles, and CPAM type 3 from acinar-like tissue. Bronchopulmonary sequestration (both intralobar and extralobar) is not in continuity with the tracheobronchial tree and is fed by an aberrant systemic artery. Congenital lobar overinflation is caused by a focal cartilaginous abnormality of the bronchial wall. Bronchogenic cyst is a unilocular malformation resulting from abnormal budding of the primitive ventral foregut. Congenital bronchial atresia is due to a focal interruption of a bronchus with associated mucocele and overinflation of the involved lung segment.

ultimately, definitively understanding whether an association between CLMs predisposition to malignancy and *DICER1* mutation exists.

Except for CLO and CBA, all other CLMs (CPAM, ILS, ELS and bronchogenic cyst) may be associated with a malignant lung lesion both in paediatric and adult patients, making none of them 'safer' than others and thus eligible for conservative treatment[19]. In the paediatric population, the CLM more frequently associated with a lung tumour is CPAM[19] whereas, in adult patients, tumours co-occur mainly with CPAM or,

Box 1

Lung development

Lung development begins at 4 weeks of gestation and can be classified into five stages[178].

Embryonic. Two lung buds appear as sacs of respiratory epithelial cells on the ventral part of the foregut[179]. Several genes are expressed at this stage: *Nkx21* (encoding TTF1) in the ventral wall, and *Sox2, Hox 5* and *Hoxb5* in the dorsal wall of the anterior foregut[38]. At 4–7 weeks, the lung buds extend and separate into branches, creating the primitive bronchi[180], while the pulmonary arteries develop from the sixth aortic arches and form a vascular plexus by growing into the mesenchyme[180]. Simultaneously, BMP4 and its antagonists Noggin, FGF10, Wnt2 and Wnt2b are expressed on the mesenchyme[181,182]. *Dicer1*, which encodes an endonuclease involved in the maturation process of siRNAs and miRNAs, generally influences embryonic development and normal cell physiology[183]. *Dicer1* inactivation in the lungs of mouse embryos shortly after the beginning of lung branching caused branching defects and prolonged ectopic cell death[184].

Pseudo-glandular. By the end of 7 weeks, repetitive sprouting forms pre-acinar airways. At 8–16 weeks, the primitive airway epithelium starts to grow and FGF10 regulates differentiation[180,185]. Sox2 and Sox9 are the main transcription factors in lung progenitor cells for branching morphogenesis and cell differentiation[186,187].

Canalicular stage. At weeks 16–25, the blood–air barrier and the terminal bronchial branches take shape. At ~20 weeks, pulmonary epithelium cells differentiate into type I and type II pneumocytes, which are crucial to lung development[188]. The pulmonary vessels also begin to proliferate and develop the mesenchymal capillary network.

Saccular stage. This stage, starting at 26 weeks of gestation, is the earliest period of lung viability and involves the formation of saccules on terminal airways. Surfactant production begins at ~26 weeks and primitive alveoli start to develop at 30 weeks[189,190].

Alveolar stage. This stage begins after birth and continues for 4–5 years with secondary septation in saccules. Alveolar ducts are divided into terminal alveoli and 85% of alveoli are formed after birth. The gas exchange surface area of the lung expands, and thoracic growth carries on until adolescence.

to a similar extent, with bronchogenic cyst[19]. In children, more than half of the CLMs are associated with a PPB, followed by adenocarcinoma in 27% of patients; in adult patients, 43.5% of CLMs are associated with adenocarcinoma, 15.2% with squamous cell carcinoma and 7.6% with bronchial carcinoid.

The onset of malignant transformation happens at any age starting from months of life up to elderly patients[19], and the interval of time between the first detection of a CLM and the discovery of an associated tumour is very variable, making a lifelong follow-up imperative in case of conservative treatment. Of note, only the pathologist can make a definitive diagnosis[19].

Mucinous cell clusters (MCCs) are pre-malignant or malignant cell clusters that occur in 75% of patients with CPAM type 1 (Fig. 2) and are not as common in CPAM types 2 and 3 (45%). MUC5AC has been identified as a valuable marker of MCCs[25], and mucinous proliferation tissue in CPAM type 1 sections have similar MUC5AC expression patterns as mucinous lung adenocarcinoma. MCCs are thought to be a precursor reservoir for potential invasive mucinous adenocarcinomas. *KRAS*, one of the most mutated genes in lung cancer, has been found to be mutated in both mucinous[26] and non-mucinous cells[27] of CPAM type 1. Sequencing analyses revealed *KRAS* exon 2 mutations in MCCs from all 18 patients examined, irrespective of whether they were diagnosed with CPAM type 1, CPAM type 3, or CPAM with an intermediate morphology between 1 and 3 (ref. 26). Furthermore, *KRAS* mutations were also found in 17 of the 25 CPAMs without MCC analysed, and the p.G12D mutation was specifically correlated with type 1 morphology. In patients harbouring both CPAM type 1 and adenocarcinomas[28], both lesions can have the same *KRAS* mutations, which is an indication that mutated *KRAS* in CPAM may confer susceptibility to cancer. In contrast to adult lung cancer, in which a *KRAS* mutation confirms malignancy, the clinical relevance of these mutations within paediatric lung specimens still needs to be investigated. If MCCs are considered a malignant or pre-malignant finding, long-term follow-up of patients with *KRAS* mutations in CPAM tissue may be indicated, especially if resection margins contain *KRAS*-positive CPAM tissue.

How CLMs are related to lung cancers is still a matter of debate. Similar to cancer cells, CPAM epithelial cells have a double proliferation index compared with normal cells and a lower susceptibility to apoptosis[29]. As CPAM is not inheritable and usually involves only one lung lobe, the mutations potentially linking CPAM with cancer are probably somatic and not germline. Despite this, the possibility of predisposing germline mutations has also been explored. De novo mutations in genes that encode proteins implicated in cancer, such as SMAD7 or KDM6A, have been found in 38.8% of patients with CPAM, providing some evidence to support prophylactic resection of CPAM[30]. Moreover, genes involved in embryonic development and cell proliferation have been found to be differentially methylated in ELS samples (*HOX3B1*, *HOXD4*, *CTNNA1*, *NR2F2*, *HSF4* and *MEIS1*), in ILS samples (*HOXA3*, *HOXB1*, *TGFB1I1*, *BRD2*, *CTNNA1*, *CTSZ*, *GPR37L1*, *S100A13*, *TSPAN3* and *FOXP2*), in CPAM type 1 (*PLD6*, *S100A13*, *MXS2* and *TXNRD1*), and in CPAM type 2 (*ZFP57* and *MEIS1*)[31]. In CPAM type 3, differentially methylated regions were identified in *MSX2* and in an intergenic region involving a *cis*-regulatory element of *PITX2*, a low methylation of which has been associated with an increased risk of lung cancer progression[32], and of *ENPEP*, which is downregulated in lung adenocarcinoma[33].

Mechanisms/pathophysiology

Congenital pulmonary airway malformation

CPAM is in direct communication with adjacent lung parenchyma and is characterized by overgrowth of terminal bronchioles to the detriment of the alveoli. CPAM usually affects one lobe, most commonly the lower ones, and multilobar or bilateral disease is less common[34]. There are several hypotheses about the mechanism of CPAM pathophysiology. One theory assumes that focal lung morphogenesis is interrupted during CPAM pathogenesis as a result of genetic defects that cause continuous expression of lung growth markers, such as SOX2 and thyroid transcription factor 1 (TTF1), together with a decreased expression of the retinoic acid enzyme RALDH1 (ref. 35). The obstructive hypothesis, which is based

on histological studies, advocates that focal obstruction of the airway tree, such as a sort of bronchial stenosis or abnormal airway peristalsis, might lead to a local increase of mediators that can trigger immune responses, such as fibroblast growth factor 10 (FGF10), interleukins and chemokines, leading to CPAM formation[36]. However, the timing of these events is poorly understood[37]. Other hypotheses on CPAM pathogenesis include the disruptive spatial patterning of epithelial cells in cysts that resemble proximal airway structures, branching morphogenesis, and imbalance between the cell cycle, cell proliferation and apoptosis[38,39] (Box 1).

Studies in transgenic murine models suggested that heterotopic overexpression of FGF7 (ref. 40) and FGF10 (ref. 41) and orthotopic expression of FGF7 (ref. 42) markedly perturb lung morphogenesis and concur in the development of CPAM. The FGF family of potent mitogens regulates cellular proliferation, migration and differentiation, with FGF7 and FGF10 being expressed in lung mesenchyme[43]. Injection of FGF10 in fetal rat lung resulted in the formation of cystic lesions, which varied depending on the developmental stage and injection location[44]. However, no alteration of FGF10 expression was found in fetal and postal-natal CPAM samples in humans, indicating that FGF10 overexpression may be a transient phenomenon during CPAM pathogenesis[45]. Cystic lung lesions are also found in mice overexpressing Krueppel-like factor 5 (KLF5)[46] or Notch1 receptor[47], and in mice lacking expression of peroxisome proliferator-activated receptor-γ (PPARγ)[48].

The most widely adopted classification scheme of CPAM is the Stocker classification[49], which combines gross and histological features and proposes that each type arises at different levels of the lung from the trachea to alveoli (Fig. 1). However, this classification has been critiqued because it brings together lesions of different aetiologies under the heading of CPAM such as type 0 and type 4 (ref. 50). Acinar dysplasia should be the preferred term for the diffuse malformation described as CPAM type 0, which is now a quite obsolete definition[51]. Acinar dysplasia is an interstitial lung disease due to bilateral impairment of bronchioles, alveolar ducts and alveoli development. The affected lung is similar to a 16-week lung in its pseudo-glandular phase with no alveolar spaces for gas exchange. It is usually lethal and associated with mutations in genes that regulate embryonic development, cell proliferation and cell differentiation, including the genes encoding FGF10, FGFR2 and the transcription factor TBX4 (refs. 52,53).

CPAM type 1 arises from the proximal bronchioles or distal bronchi (Fig. 1). CPAM type 2 lesions are believed to arise secondary to bronchial obstruction and may contain *KRAS*-mutated cells[27,37,54–56]. CPAM type 3 is believed to originate from acinar-like tissue and has been associated with activating *KRAS* mutations or mutations in other genes involved in cell cycle regulation and growth; 50% of CPAM type 3 have a *KRAS* mutation, most commonly p.G12V. Overall, the formation of CPAMs type 1 and type 3 seems to be driven by mosaic *KRAS* mutations arising in the lung epithelium early in development and places them within the growing cluster of mosaic RASopathies. Moreover, among the 351 genes that were identified as differentially expressed in paediatric CPAM, BPS or hybrid lesions compared with unaffected tissue of the resected lobe, genes in the Ras complex, PI3K–AKT–mTOR and mTOR signalling pathways as well as in Myc transcriptional targets were significantly enriched[57]. It has been argued that CPAM type 4 is identical to type 1 PPB[58] and should be considered a PPB, which is generally not diagnosed prenatally[23,51,59,60].

Bronchopulmonary sequestration

BPS is a hamartomatous mass of non-functioning lung tissue, and the mechanisms involved in BPS formation generally remain unknown. The role of *Hoxb5* has been demonstrated in the developing mouse lung[61]. Expression of the homeobox protein Hoxb5 is strong during airway branching and becomes negligible near term and later. High expression of Hoxb5 protein has been found in a newborn with BPS and this misregulation might be involved in BPS pathogenesis[61]. BPS lesions are not in continuity with the tracheobronchial tree and are supported by an aberrant systemic artery[37]. ILS, which appear within the visceral pleura, represent 75% of BPS lesions and are often localized in the lower lobes. Even though the abnormal lung parenchyma is non-aerated, some collateral ventilation is supported by the pores of Kohn and channels of Lambert of the adjacent lung tissue[37]. Consequently, ILS are at increased risk of bacterial seeding and pneumonia or other complications[34]. ILS are usually fed by a single artery most commonly coming from the descending thoracic aorta and branching to the lower lobe after passing through the inferior pulmonary ligament. Multiple arterial supply has been described in 16% of cases[62]. The venous drainage is most commonly to the left atrium through the pulmonary veins[62].

ELS correspond to 25% of BPS lesions and are covered by a distinct pleura. ELS have one or, in 20% of cases, more than one feeding artery, usually stemming from the thoraco-abdominal aorta and systemic venous drainage that is separated from normal lung parenchyma.

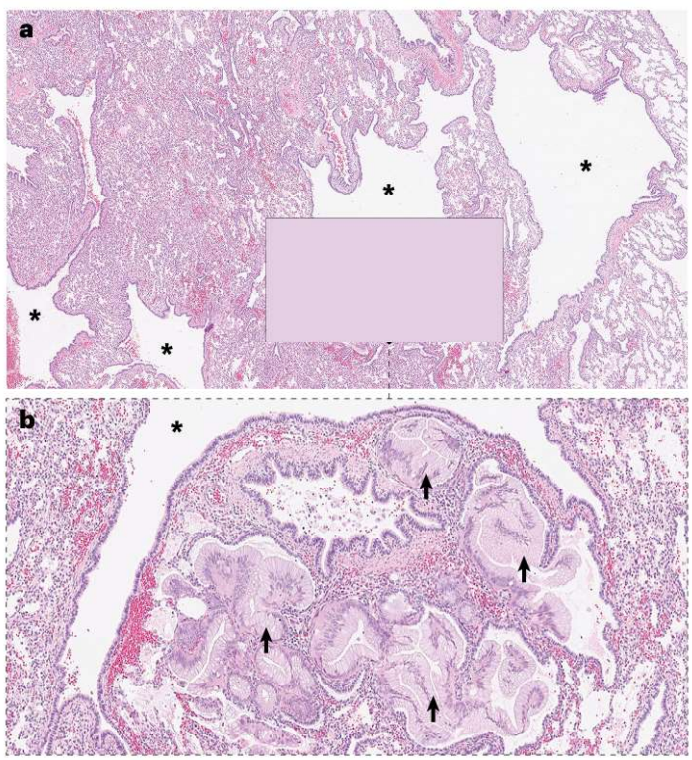


Fig. 2 | Histology of CPAM type 1 with mucinous cell clusters. a,**b**, Haematoxylin and eosin-stained low power (2.5×; part **a**) and high power (10×; part **b**) micrographs of congenital pulmonary airway malformation (CPAM) type 1 lesion demonstrating large cystic spaces (*) lined by non-atypical respiratory and cuboidal epithelium, surrounded by alveolar tissue with collapsed but apparently normal morphology, with focal proliferation of columnar mucinous cells (arrows). These mucinous proliferations as well as the adjacent cystic spaces were shown to contain a *KRAS* exon 2 c.35G>A (p.G12D) mutation by next-generation sequencing.

Glossary

Acinar dysplasia
A rare malformation characterized by growth arrest of the lower respiratory tract and complete absence of gas-exchanging units, resulting in critical respiratory insufficiency at birth.

Acinar-like tissue
A tissue composed of polarized epithelial cells rich in rough endoplasmic reticulum and characterized by an abundance of secretory zymogen granules.

Channels of Lambert
Microscopic collateral airways between the distal bronchiolar tree and adjacent alveoli.

Congenital anomalies
Structural or functional anomalies occurring during intrauterine life and affecting an estimated 6% of global live births (WHO definition).

Congenital diaphragmatic hernia
A defect in the diaphragm causing the herniation of abdominal contents into the thoracic cavity, resulting in lung hypoplasia and altered pulmonary vascular development.

Epithelial–mesenchymal interaction
A series of programmed, sequential and reciprocal communications between the epithelium and the mesenchyme, with its heterotypic cell population, that result in the differentiation of one or both cell populations.

EXIT-to-resection
In the EXIT-to-resection procedure, a hysterotomy is performed to exteriorize the fetal head and torso enabling orotracheal intubation and placement of peripheral IV; the lung malformation can be resected while the fetus is still on placental support[34].

Foregut duplication cysts
Benign developmental anomalies that contain foregut derivatives.

Hydrops
Abnormal interstitial fluid collection in two or more compartments of the fetal body.

Lung compliance
A measure of the expansion of the lung.

Mediastinal shift
The deviation of mediastinal structures towards one side of the chest cavity.

Oesophageal duplication
Separate masses along or in continuity with the native oesophagus.

Polyhydramnios
A condition that occurs when too much amniotic fluid builds up during pregnancy.

Pores of Kohn
Small communications between adjacent pulmonary alveoli that provide a collateral pathway for aeration.

Thoraco-amniotic shunt
A shunt that drains fluid from the lung into the amniotic sac to treat pleural effusion, for example, in congenital pulmonary airway malformations.

Tidal volumes
The amount of air that moves in or out of the lungs with each respiratory cycle.

Tricuspid annular plane systole excursion
A scoring system used with non-invasive Doppler echocardiography to determine right ventricular function.

In 80% of cases, systemic venous drainage occurs through the azygos or hemiazygos system or through the vena cava to the right atrium[62]. Infections are less common in ELS as they are not connected with the tracheobronchial tree, and presenting symptoms of ELS are mainly associated with abnormal systemic vascularization, which sometimes leads to high-output congestive heart failure as a result of the right-to-left shunt, or to torsion of the vascular pedicle. ELS is usually found in the thoracic cavity but it can also develop below the diaphragm in the abdomen or within the diaphragm[37].

CPAM–ILS and CPAM–ELS hybrid or mixed lesions found in the paediatric population share histopathological features of CPAM type 1 and type 3 and of CPAM type 2, respectively, and rely on systemic blood supply[63,64]. Such lesions are distinct from acquired lesions diagnosed in adults following lower lobe infections that cause the cystic degeneration of the parenchyma and the proliferation of systemic arteries entering the lung through the pulmonary ligament or across the pleura[62].

Congenital lobar overinflation

CLO is caused by a focal cartilaginous abnormality of the bronchial wall, which creates a valve effect and consequent overinflation of a pulmonary lobe after birth[65]. The bronchial narrowing may be caused by intrinsic factors, such as the absence of bronchial cartilage, bronchial stenosis or bronchomalacia, or by an extrinsic cause such as a vascular sling[66]. In ~50% of patients, however, CLO is idiopathic and a clear aetiology cannot be identified[66]. The left upper lobe and the right middle lobe are most commonly affected by CLO.

Bronchogenic cyst

Bronchogenic cysts are unilocular malformations resulting from abnormal budding of the primitive ventral foregut. Bronchogenic cysts contain cartilaginous tissue, smooth muscle and bronchial glands, all lined by ciliated columnar epithelium. Most bronchogenic cysts are localized in the mediastinum adjacent to the trachea or the mainstem bronchi (subcarinal space) but, sometimes, they can be intrapulmonary or appear outside the chest, in the areas of the neck, the abdomen or the skin[34,67]. The pathophysiology of bronchogenic cysts is still unknown. Bronchogenic cysts can be asymptomatic. Mediastinal bronchogenic cysts do not communicate with the tracheobronchial tree but they contain mucus and may enlarge or compress the bronchi, causing dyspnoea[67]. Intrapulmonary bronchogenic cysts are connected with the tracheobronchial tree and can lead to respiratory symptoms in newborns or infants or to infection in children as a result of air trapping[67].

Congenital bronchial atresia

CBA stems from a focal interruption of a lobar, segmental or subsegmental bronchus and is associated with the presence of a mucocele and overinflation of the involved lung segment. The presence of the mucocele is pathognomonic and results from mucus accumulation following airway obstruction[68]. CBAs are hypothesized to occur after the sixteenth week of gestation, probably due to intrauterine ischaemia. The apicoposterior segmental bronchus of the left upper lobe seems to be most commonly affected by CBA[68]. Proximal CBA is located at the level of the mainstem or the proximal lobar bronchi and it is almost always fatal during pregnancy or immediately after birth[65]. Peripheral CBA involves the segmental or subsegmental bronchi and has also been associated with other prenatal lung malformations, including CPAM, BPS and CLO[65], as part of the histopathological spectrum of these CLMs. In this Primer, we discuss peripheral CBA, where it presents as an isolated lesion[65].

Diagnosis, screening and prevention

Clinical presentation

Prenatally diagnosed CLMs have highly variable clinical presentation, ranging from lack of any symptoms to respiratory distress at birth[15,34]. The latter is a rare event that occurs in <10% of patients mostly as a

result of a mediastinal shift caused by a CLO or a large CPAM[15,34] and requires emergency surgery. After birth, the progressive hyperinflation of the lobe affected by CLO may result in a mediastinal shift and consequent compression atelectasis of normal lung parenchyma[69]. Acute and rapidly worsening air trapping at birth can lead to severe respiratory symptoms and the need for surgery. In some instances, hyperinflation of the lobe is slower and accounts for the delayed onset of respiratory symptoms within the first weeks of life[69]. However, some patients have minimal pulmonary symptoms or are completely asymptomatic and are therefore managed with serial observation[34]. Most commonly, however, children with prenatally diagnosed CLMs remain asymptomatic postnatally[70] and admission to an intensive care unit is not justified in an asymptomatic newborn[34].

Nearly half of patients who are asymptomatic at birth develop symptoms in their first year of life, with a peak at a median age of 2 years[71]. Long-term follow-up has revealed that most infants with CLM develop symptoms[71,72]. The most common symptoms are respiratory infections, pneumonia, fever, chronic cough, pneumothorax and respiratory distress. The incidence of respiratory infections in children with CLM is not clearly defined and varies across studies at between 5% and 86%[71,73,74]. High-output cardiac failure is a rare complication resulting from large systemic feeding vessels[37].

Prenatal screening and diagnosis

Fetal ultrasonography. Although CPAM, BPS, CLO, bronchogenic cyst and CBA are distinct pathologies, their embryology and imaging phenotyping overlap[1] and they also share some common clinical and histological features[64]. The prenatal diagnosis of CLMs relies on the cystic or solid appearance of space-occupying lesions within the fetal thorax or the abnormal size of the lungs and consequent deviation of the heart from its normal 45° position (Fig. 3). According to the Adzick classification for fetal ultrasonography, CLMs are described as either macrocystic lesions that present as single or multiple cysts of >5 mm or microcystic lesions with solid appearance that feature cysts of <5 mm (ref. 75).

CLMs are easily detected during routine prenatal ultrasonographic examination at 18–22 weeks of gestation. The differential diagnosis includes congenital diaphragmatic hernia, oesophageal duplication, foregut duplication cysts and other thoracic masses such as pericardial teratoma. CLMs usually increase in size between 20 and 26 weeks of gestation before reaching a plateau by 29 weeks of gestation[76]. Later, the decrease in size of CLMs seems to be related not only to growth of the fetus but also to the transition from the canalicular to saccular stage of lung development (Box 1), with consequent changes in rates of proliferation and apoptosis of epithelial and mesenchymal cells[77]. CLMs become isoechoic to normal lung tissue late in gestation, and this can be mistakenly considered as the disappearance of lesions. For this reason, it is imperative to perform a CT angiography (CTA) scan after birth to confirm or exclude the presence of a CLM. Amniocentesis is not recommended in pregnancies with a diagnosis of CLM if a solitary lung lesion is identified. Vaginal delivery at a local birthing centre without neonatal intensive care or paediatric surgical support is safe for fetuses with small lung lesions[15].

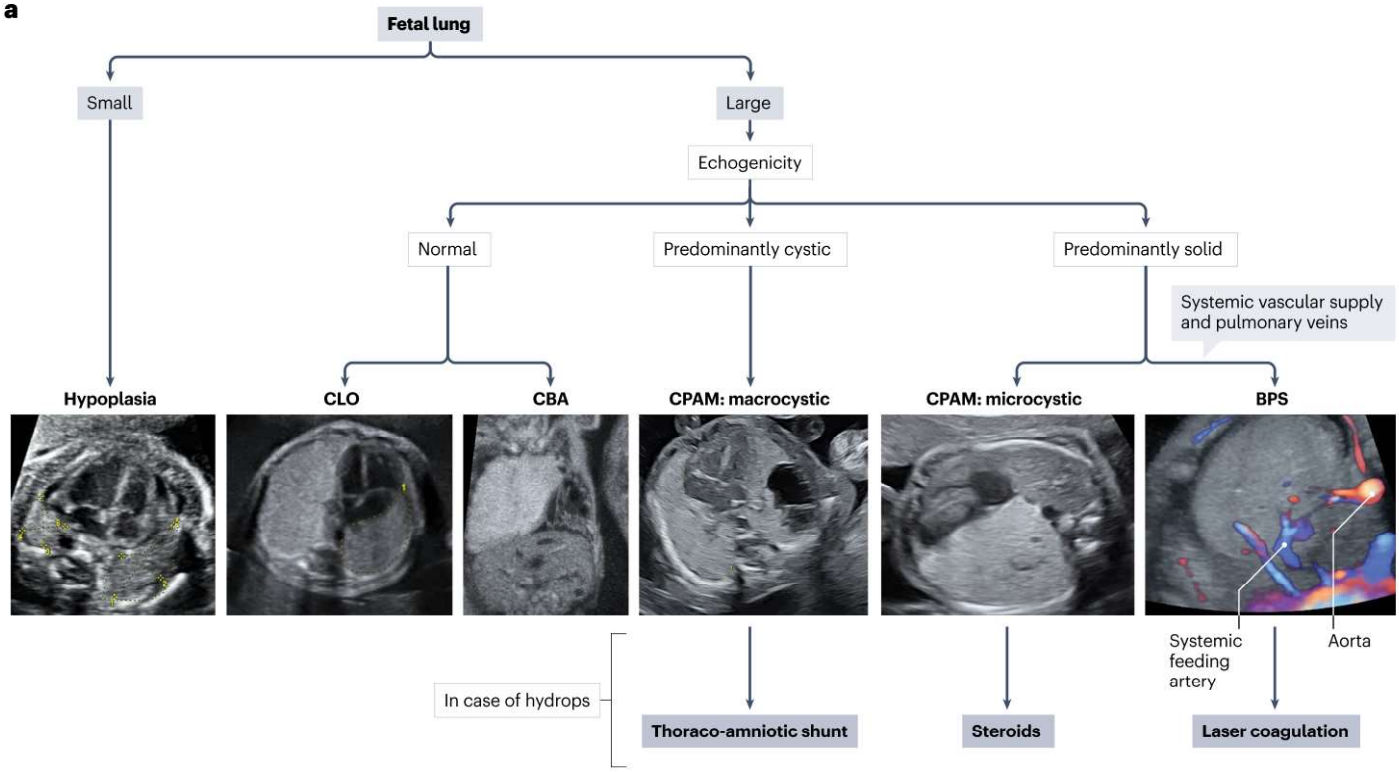
CPAM and BPS are the two CLMs most commonly diagnosed in utero as intrathoracic, usually unilateral, cystic or solid masses[78]. CPAM is usually recognized at mid-gestation as a multilocular lesion with cysts from a few millimetres to 10–12 mm in size (macrocystic type) or as a well-defined, homogeneously hyperechogenic mass (microcystic type)[78]. In both cases, the heart is usually pushed to the contralateral side[78]. BPS appears as a well-defined homogeneously hyperechogenic mass that is indistinguishable from the microcystic type of CPAM[78]. However, exploration with colour Doppler ultrasonography can help identify any aberrant feeding artery arising from the aorta, and this is specific to BPS. 3D and 4D ultrasonography may provide greater information regarding the spatial relationship, volume and vascular feeding of both CLMs[79]. A large CPAM can grow and cause mediastinal shift with consequent oesophageal compression, pulmonary hypoplasia, polyhydramnios and obstruction to venous return, leading to hydrops[80] (Fig. 3). Thus, it is recommended to monitor CLM growth by serial calculation of the CPAM volume ratio (CVR)[81].

ILS hydrops may develop in the fetus because of abnormal systemic arterial blood supply with an increase of venous drainage via the pulmonary veins, leading to 'left-to-left' shunting, which sometimes results in high-output cardiac failure. Therefore, it is recommended to assess cardiac function, for example, based on tricuspid annular plane systole excursion, every 2 weeks since the diagnosis of hydrops, usually at around 22–24 weeks of gestation, to identify haemodynamic deterioration[82] (Fig. 3).

CLO is identified only rarely via prenatal screening mainly because of the isoechoic appearance and lack of mediastinal shift in utero[69]. CLO appears in fetal ultrasonography as uniformly enlarged lung, mildly hyperechoic, without cysts or systemic arterial supply[79]. The identification of a tubular cystic hilar structure consistent with a dilated bronchus and prominent oblique lung fissure at 2D and 3D ultrasonography may hint towards the correct diagnosis[79] (Fig. 3).

Mass size, rather than CLM type, is the major predictor of perinatal outcomes[15,83]. CVR, the ratio of the 3D size of the lesion to the fetal head circumference, is the most commonly used metric for CLM mass[84] (Fig. 3). The risk of developing fetal hydrops is ~80% for fetuses with a CVR exceeding 1.6, and a CVR increase during pregnancy has been associated with increased rates of prenatal intervention and adverse postnatal outcomes[85,86]. CVR has been associated with the development of hydrops, neonatal respiratory distress (NRD) and increased rates of oxygen supplementation, mechanical ventilation, and resection at birth[15]. In addition, high CVR at diagnosis or high maximum CVR values were predictive of risk of NRD for both term and preterm infants[87] but consensus on a precise cut-off value is lacking[88]. One cohort study showed that a CVR of ≤0.39 measured at between 25 and 30 weeks of gestation predicts a low probability of the need for respiratory support at birth but does not rule out respiratory problems later on[89]. The low probability of NRD (<10%) for a maximum CVR of <0.40 supports this cut-off value[87]. A CVR of >0.84 seems to be a reliable predictor of respiratory morbidities such as respiratory distress, recurrent infections, cough and the need for surgical resection at birth[90,91] (Fig. 3).

Fetal MRI. The merit of MRI for the prenatal diagnosis of CLMs remains controversial[34]. MRI can be used to accurately assess the location, size and mass effect of CLMs[92,93], and one study has shown the superiority of MRI against ultrasonography in identifying vascular supply[92]. However, in fetuses with small lung lesions, the limited additional information provided by prenatal MRI is not sufficient to amend management plans. For this reason, MRI is only selectively recommended, for example, when a lung lesion is not clearly defined at prenatal ultrasonography or in the presence of a large CLM. MRI might help to characterize the malformation or to prepare a treatment plan if prenatal management or early neonatal resection are needed[88,92]. In such cases, the best timing for fetal MRI is between 24 and 30 weeks of gestation[94].


a
Fetal lung
Small
Large
Echogenicity
Normal
Predominantly cystic
Predominantly solid
Systemic vascular supply and pulmonary veins
Hypoplasia
CLO
CBA
CPAM: macrocystic
CPAM: microcystic
BPS
Systemic feeding artery
Aorta
In case of hydrops
Thoraco-amniotic shunt
Steroids
Laser coagulation

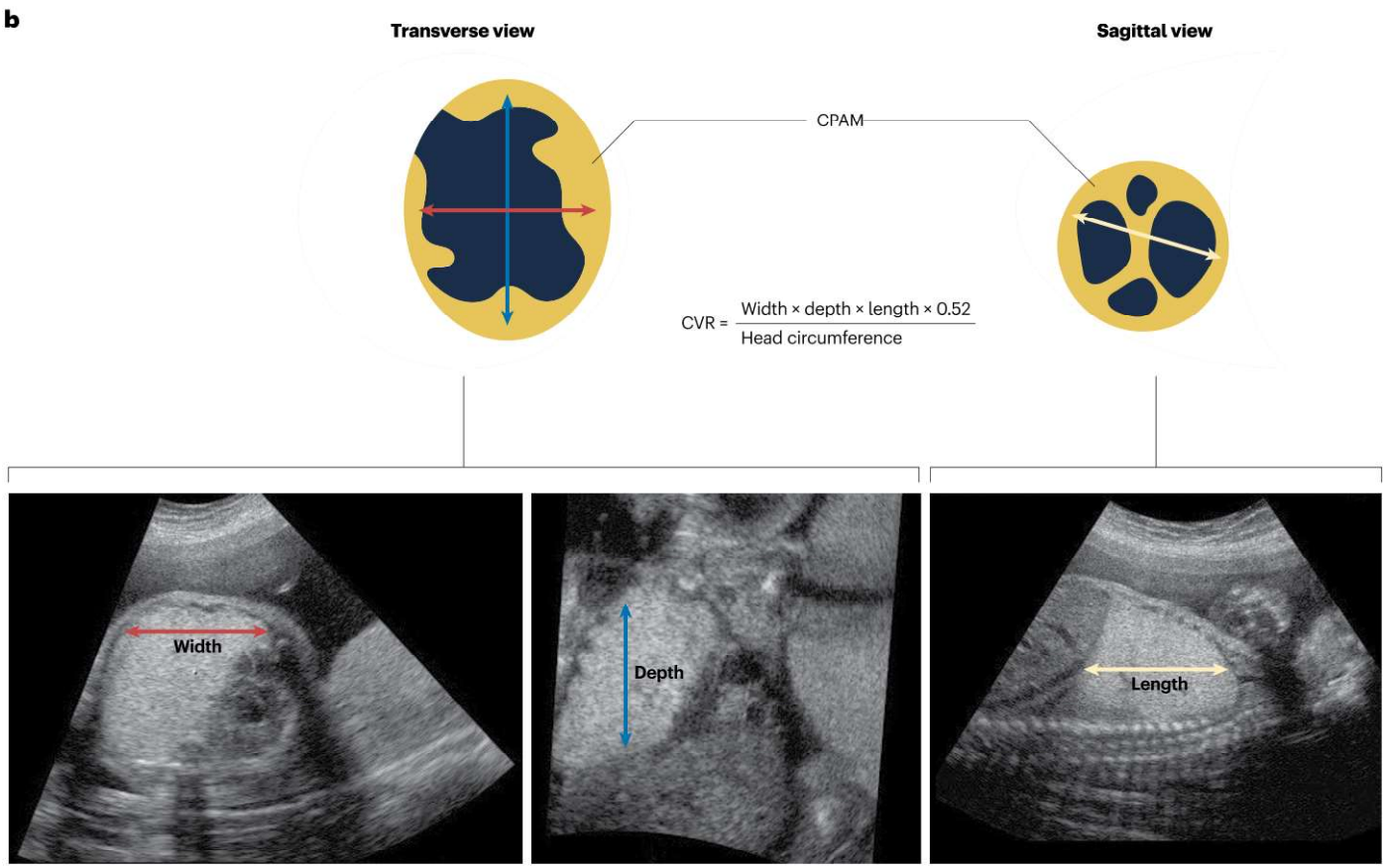

b
Transverse view
Sagittal view
CPAM
CVR = Width × depth × length × 0.52 / Head circumference
Width
Depth
Length

Fig. 3 | Prenatal CLM diagnosis and management. a, Ultrasonographic prenatal diagnosis of congenital lung malformation (CLM) relies on the size of the lungs and the identification of space-occupying lesions, either solid or cystic, within the fetal thorax. Congenital pulmonary airway malformation (CPAM) may present as either a multilocular lesion with cysts (macrocystic type) or as a well-defined homogeneously hyperechogenic mass (microcystic type). Bronchopulmonary sequestration (BPS) appears as a homogeneously hyperechogenic mass with an aberrant feeding artery arising from the aorta. Congenital lobar overinflation (CLO) and congenital bronchial atresia (CBA) appear as uniformly enlarged lung, mildly hyperechoic, without cysts or systemic arterial supply, like microcystic CPAM. CPAM and BPS can cause fetal hydrops, which would benefit from the insertion of a thoraco-amniotic shunt (macrocystic CPAM), administration of steroids (microcystic CPAM) and vascular laser ablation (BPS). **b**, Illustrative diagram of CPAM volume ratio (CVR) and its calculation on prenatal ultrasonography images. CVR is a 3D (width: red arrow; depth: blue arrow; length: yellow arrow) sonographic indicator of the mass volume normalized for gestational age to evaluate fetuses at risk of developing hydrops.

Postnatal diagnosis

CT angiography. Postnatal chest CTA at 2 months of age is essential for confirming a prenatal diagnosis of CLM (Fig. 4) and to outline a management plan. Chest CTA is the current gold standard for the postnatal evaluation of CLMs due to its ability to provide the highest spatial resolution and sensitivity[95,96]. The scan range of chest CTA should cover the anatomical area from the thoracic inlet to the mid-abdomen to enable full capture of the extent of any aberrant vasculature, which may arise or extend below the diaphragm[97]. The CTA protocol should be tailored to the weight of a patient in accordance with the ALARA principle and include thyroid function monitoring to promptly detect any temporary thyroid dysfunction[98].

Third-generation CT scanners use a lower amount of radiation and have a rapid acquisition speed that overcomes the need for sedation[95]. They deliver diagnostic-quality images in >95% of patients[95,96], regardless of age or compliance with breathing instructions. Structured assessment of CTA results[99] can consistently provide precise information about the size, location and other characteristics of CLMs[100] that are crucial for surgical planning.

Chest radiography. Chest radiography is a first-line screening tool due to being non-invasive and cost-effective. However, a prenatally diagnosed CLM should never be ruled out in a newborn based on chest radiography only as it fails to detect CLM in 50% of patients[101–103], and the information it provides fails to predict the potential onset of symptoms or to inform the surgical plan[95] (Fig. 4). In paediatric patients that present with recurrent pneumonia in the same lung lobe but lack a prenatal diagnosis of CLM, certain radiographic features, such as persistent opacities or radiolucency, can raise suspicion of an underlying undiagnosed CLM[104]. In case of strong clinical suspicion of CLM after the complete healing of pneumonia, further imaging evaluation using cross-sectional techniques, such as CTA or MRI, is necessary to obtain a comprehensive and accurate diagnosis (Figs. 4 and 5).

Chest radiography can also be applied to assess potential complications of CLM surgery such as pneumothorax, bleeding and infections[95]. In previously asymptomatic children with CLM who developed new symptoms, chest radiography is often the first imaging modality used to evaluate the cause of these symptoms[95] and assess them as potential complications of BPS or CPAM, in the case of infections, and CLO or bronchogenic cyst, in the case of progressive hyperinflation.

Lung ultrasonography. Lung ultrasonography has limited application in the detection of CLMs after birth as ultrasound waves cannot penetrate normally aerated lungs and can only be used to image peripheral lung lesions[95,105]. Lung ultrasonography can still be a cost-effective method for the diagnosis of complications in paediatric patients with respiratory distress[106] or infection as the consolidation of the lung parenchyma in these patients makes the visualization of the CLM easier.

MRI. Chest MRI has the potential to replace CTA for the assessment of CLMs in the future[93,107], especially in medical centres that have expertise in chest MRI techniques[93]. However, in current practice, surgical plans cannot be based entirely on MRI as CTA provides superior quality images of lung parenchyma, especially in infants. In addition, sedation is required for infants and young children between 6 months and 5 years of age undergoing MRI[95,108].

Chest MRI protocols have the added advantage of not requiring contrast agents to visualize the vascular anomalies associated with CLMs[109]. In cases of CLMs with abnormal blood vessels, chest MRI can be combined with cardiac MRI to assess blood flow and shunting[95]. There are several clinical scenarios in which chest MRI may be used to assess CLMs, including follow-up of a previously identified CLM to avoid repeated exposure to radiation, evaluation of a mass in an atypical location or complementary characterization when CTA is incomplete[93].

Histopathology

Histopathological assessment of lung tissue is necessary to confirm a diagnosis of CLM and to identify the CLM subtype.

Congenital pulmonary airway malformation. CPAM type 1 appears as a cystic lung lesion, with cyst size ranging from <0.5 cm to >7 cm in the greatest dimension. CPAM type 1 cysts are lined by ciliated cuboidal to stratified columnar epithelium, occasionally featuring cartilage in the cyst wall, and are interspersed within a lung parenchyma with enlarged and simplified alveoli[54,110]. Multiple connections are observed between the thick cyst wall and adjacent alveolar wall, and epithelial complexity, including papillary projections, may occur[54,110]. Some CPAM type 1 lesions may have solid-appearing areas with features of both type 1 and type 3 CPAM. In CPAM type 2, there are both identifiable cysts lined by ciliated columnar epithelium and mildly malformed alveolar-type spaces[54,110]. Cysts can measure up to 2.5 cm in the greatest dimension and are also interspersed within normal-appearing lung parenchyma. Striated skeletal muscle occasionally appears in the septa between cysts. CPAM type 3 lesions have a solid, often lobulated appearance, and are well-demarcated from uninvolved lung parenchyma characterized by small irregularly shaped airway spaces lined by ciliated cuboidal to columnar epithelium[54,110]. Surrounding septa often appear thickened, with prominent mesenchyme and cuboidal epithelium[54,110].

Bronchopulmonary sequestration. BPS is defined by an anomalous systemic vascular supply and sequestration from the tracheobronchial tree. The systemic feeding vessel is usually identified only radiologically, but it may still be identifiable in intact gross specimens. The BPS parenchyma has a variable macroscopic appearance, ranging from grossly normal to cystically altered[110]. Histologically, systemic artery branches may appear thickened with some

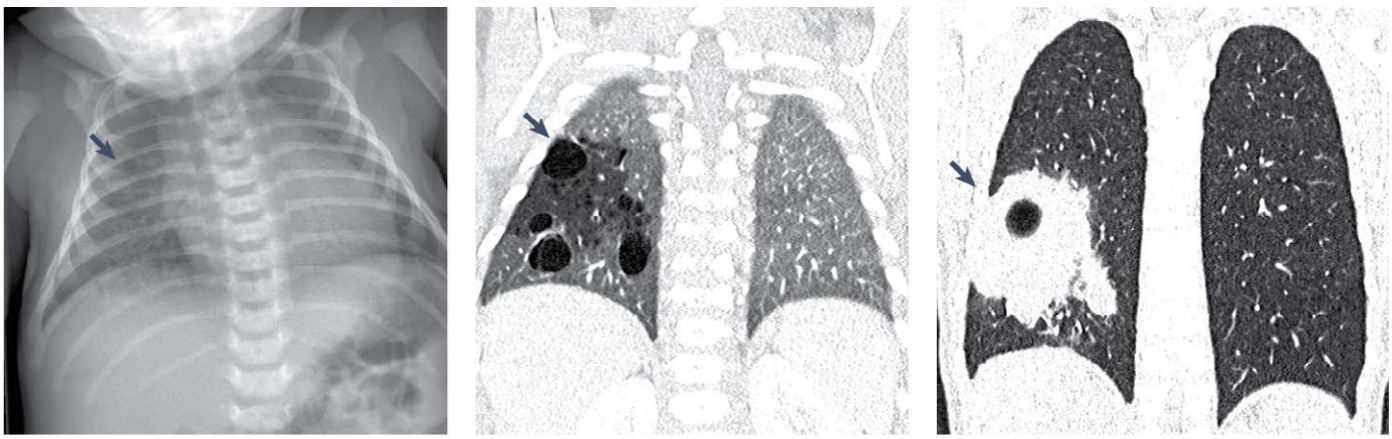


Fig. 4 | Asymptomatic patient with CPAM becoming symptomatic. **a**, Anterior–posterior chest radiography at birth shows some radiolucent round abnormalities in the perihilar region of the right lung (arrow). **b**, Coronal lung window of chest CT angiography at 6 months shows a multicystic lesion (arrow) with cysts <2 cm surrounded by low-density lung parenchyma, which is consistent with congenital pulmonary airway malformation (CPAM) type 2. **c**, CT angiography at 5 years old of the same patient admitted with signs of pneumonia. The coronal CT reformat shows consolidation (arrow) of the lung parenchyma surrounding the cystic component of the CPAM.

features that are characteristic of pulmonary hypertension in older patients[111]. All patients have at least mild parenchymal maldevelopment with enlarged and simplified alveoli[63,64]. Pools of mucin and foamy intra-alveolar macrophages may suggest the presence of mucostasis[50]. Foci of skeletal muscle may be seen in septa between larger cysts[110]. Prominent lymphangiectasia is seen in a subset of extralobar bronchopulmonary sequestrations[110].

Congenital lobar overinflation. In CLO, tissue architecture is maintained, unlike in acquired emphysema. However, lack of acinar maturation with age and overinflated alveoli are seen[110]. In many CLOs, there are normal numbers of radial alveoli at birth, but with acinar development arrested in the postpartum period[110]. In the hypo-alveolar and poly-laveolar subtypes fewer or more than the expected number of alveoli are present, respectively[112].

Bronchogenic cysts. Bronchogenic cysts present as unilocular cysts filled with serous or mucinous material, lined by respiratory-type epithelium, reminiscent of the bronchial wall with variable amounts of seromucinous glands, cartilage and smooth muscle[110]. Secondary changes related to previous infection or procedures may include acute and chronic inflammation with epithelial denudation or squamous metaplasia and evidence of haemorrhage with cholesterol clefts and/or haemosiderophages as well as variable fibrosis[110].

Congenital bronchial atresia. Surgical specimens of CBA have an atretic bronchus with distal pink hyperaerated lung with occasional subpleural blebs[113]. There is no proximal or central tracheal communication of the atretic bronchus, whereas distal to the atresia there is cystic dilatation of the bronchus, sometimes amounting to a mucocele, that contains plugs of desquamated tissue and mucus as an unvarying component[113]. The blind end of the proximal or distal bronchus is lined with bronchial epithelium without scar formation or granuloma[68]. Microscopic examination of the distal pulmonary parenchyma is essentially normal except for dilatation of alveoli and hypoplasia as evidenced by a reduced number of alveoli per unit area[113].

Management

In utero management

Maternal steroids. The first-line therapy for giant microcystic lesions (CVR >1.6) and hydrops or impending hydrops is maternal administration of two doses of systemic steroids[114]. This treatment is most effective before the twenty-sixth week of gestation[115,116]. It has been suggested that steroids act by speeding the passage from the canalicular to saccular stage of lung development[34] (Fig. 3). However, steroids show no efficacy in fetuses with macrocystic lesions[117].

Thoraco-amniotic shunts. When hydrops complicates a pregnancy with large fetal lung lesions containing a dominant macrocyst, the insertion of a thoraco-amniotic shunt (TAS) (Fig. 3) has been demonstrated to decrease the mass effect of the malformation, improving hydrops and increasing fetal survival[114]. This ultrasonography-guided minimally invasive procedure can rely on double pigtail catheters to minimize dislodgement. However, it carries the risk of premature rupture of membranes, preterm labour, chorioamnionitis, shunt occlusion or dislodgment, and chest wall deformities[114].

Fetal surgery. The introduction of steroid therapy has considerably limited the need to recur to fetal surgery in case of severe hydrops before the third trimester[118]. Similarly, indications for EXIT-to-resection management with the aim of creating space for the lung to function postnatally are very rare and considered for large lesions with CVR >2 and persistent mediastinal shift[118].

Fetal management of BPS. Expectant management of fetuses with BPS and associated hydrops can lead to pulmonary hypoplasia and consequent poor prognosis[119,120]. However, the use of TAS has proved helpful in decreasing hydrops and neonatal death[34]. Laser coagulation of the feeding vessel contributes to a decrease in volume of the malformation[121] (Fig. 3). A multicentre study[122] has demonstrated that laser ablation interrupting blood supply to the malformation helps to achieve better perinatal outcomes compared with TAS, including longer gestational age and less frequent postnatal surgery.

Postnatal management

Surgical treatment. The superiority of a thoracoscopic approach over thoracotomy has been extensively proven[123–127]. When compared with open thoracotomy, a thoracoscopic approach is minimally invasive, with improved visualization, feasible regardless of patient size and weight[124,128], and its decreased invasiveness results in less pain, shorter hospital stay, and decreased long-term morbidity, including a decreased risk of chest wall deformity, shoulder girdle weakness and scoliosis[129,130]. Moreover, the magnification provided by thoracoscopy enables better visualization, especially of fissures and vessels[130].

Standardization of the thoracoscopic technique, including an anterior approach to the patient and vessel sealing to manage the pulmonary vessels, has resulted in a reproducible and consistent method that can be taught worldwide. Most procedures are elective and, therefore, should be scheduled in centres experienced and trained to perform this minimally invasive procedure[125]. Moreover, lobectomy is considered safer than sublobar or segmental resections, as it is not possible to accurately determine the limit between CLM and normal parenchyma in the latter procedures and incomplete resections have been demonstrated to result in complications such as pneumothorax[131]. Thus, thoracoscopic lobectomy in children for CLMs should be considered the standard of care[123–127].

The timing of resection is debatable, with some preferring earlier surgery, by 4 months of age (Fig. 5), and some as late as 1 year of age, although delayed resection has not shown improved outcomes[132]; in older infants, substantial adenopathy and inflammation in the fissures and around the pulmonary artery can lead to more difficult identification and safe division of these vessels (Fig. 4). Data suggest earlier resection is associated with shorter operative times, hospital stays and reduced rates of inflammation in specimens[128,133–135]. Early resection may also reduce the likelihood of pre-operative respiratory infections, which can distort tissue planes, create thick adhesions and complicate surgery, causing more frequent conversion from a minimally invasive approach to open surgery because of impaired visualization and difficult lung mobilization[136,137]. Moreover, the same patients with pulmonary infections before surgical treatment had an increased incidence of postoperative infections[136].

In asymptomatic CLO or CBA, there is agreement that no surgical treatment is required[138] and serial observation is adequate[34]. However, if CLO or CBA become symptomatic due to progressive air trapping of the affected lobe or infection, respectively, surgery is performed.

A sublobar anatomical resection is only relevant if there is multilobar disease.

Management of asymptomatic CLMs. Prenatally diagnosed CLMs that are symptomatic at birth or become symptomatic during the neonatal period are managed with surgical resection. However, there is still an unresolved controversy among paediatric surgeons about the management of prenatally diagnosed CPAM, BPS or bronchogenic cysts that are asymptomatic after birth. Most paediatric surgeons are still in favour of prophylactic surgical resection of asymptomatic CLMs (Fig. 5). However, some specialists consider conservative (non-operative) management as an alternative to surgical resection, unless symptoms and complications emerge[73,139,140].

Three lines of argumentation are used by clinicians favouring a conservative management approach. First, it has been suggested that unnecessary invasive surgery and general anaesthesia may have negative effects on long-term neurodevelopment, and some potentially serious or even life-threatening complications in infants and children[8,141–144]. Second, it has been argued that most asymptomatic patients remain asymptomatic during childhood[73,74,145–147]. Third, professionals favouring conservative non-operative management consider the risk of malignancy as being small[17].

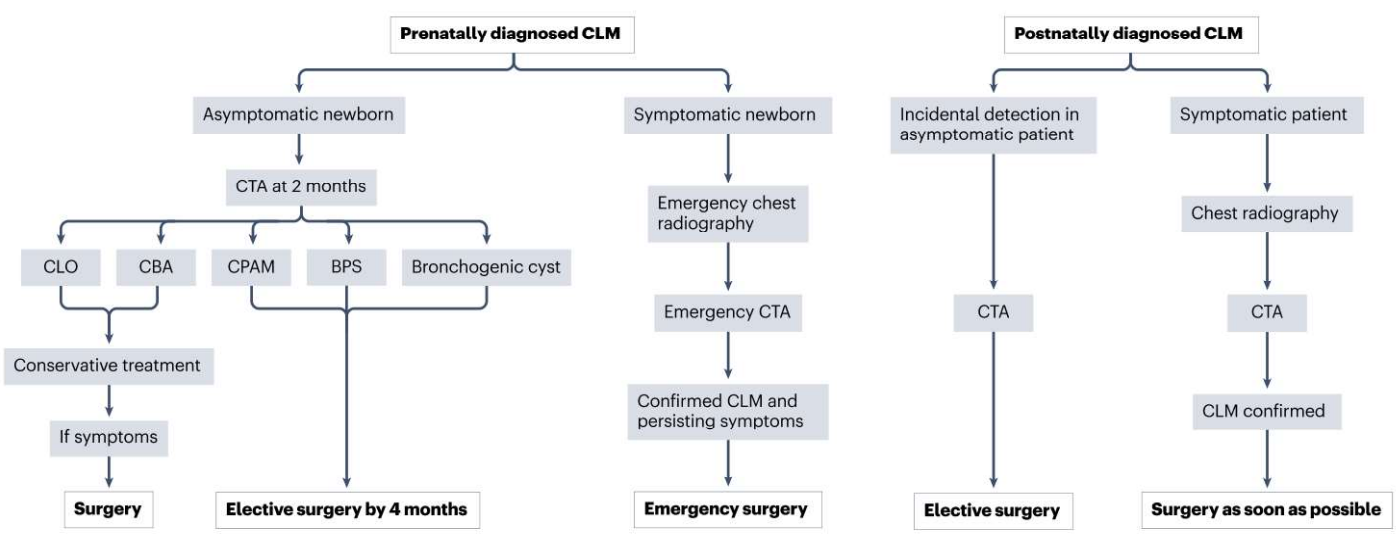


Fig. 5 | Algorithm of postnatal diagnosis and surgical management in asymptomatic and symptomatic CLM. In asymptomatic prenatally detected congenital lung malformations (CLMs), the diagnosis must be confirmed with CT angiography (CTA) at 2 months. Asymptomatic congenital lobar overinflation (CLO) and congenital bronchial atresia (CBA) can be managed conservatively. However, if CLO or CBA become symptomatic due to progressive air trapping of the affected lobe or infection, respectively, surgery is performed. By contrast, patients with asymptomatic congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS) and bronchogenic cyst undergo elective surgery by 4 months of age. A symptomatic newborn needs emergency chest radiography and CTA to confirm prenatal diagnosis and, in case of persistence of symptoms, undergoes emergency surgery. In case of incidental detection of a previously undiagnosed CLM, a CTA is needed to confirm the diagnosis and elective surgery is planned. When a CLM is suspected in a symptomatic patient, chest radiography and CTA are needed to confirm the diagnosis and surgery is planned as soon as possible.

However, the thoracoscopic approach has transformed the procedure into a mini-invasive one[129,130]. In addition, normal neurodevelopment outcomes have been demonstrated for children who undergo surgical removal of a CLM in comparison with their healthy peers[148], and early prophylactic elective surgery can facilitate compensatory lung growth[70]. Moreover, records of long-term follow-up for the emergence of symptoms later in life are lacking. Of the patients with CLMs that have been followed up until adulthood and patients who have been diagnosed with CLM in adulthood (Box 2), 80% have become symptomatic and often present with acute onset of symptoms at diagnosis[149–152]. In addition, pre-operative infections make surgery more challenging and increase the rate of conversion to thoracotomy[136]. Finally, even though the true incidence of malignancy in patients with CLMs remains unknown, lung cancer may appear at any age and is accompanied by non-specific symptoms of respiratory infections that may be missed[19], whereas radiological imaging fails to predict the risk of malignancy or provide an early diagnosis of cancer[19].

The real conundrum in following a conservative approach is to design a clear follow-up programme for patients in terms of frequency, duration and methodology. Chest radiography is inadequate to detect malignant transformation in CLMs[95]. Repeated exposure to chest CTA poses a risk of iatrogenic malignancy[153], precluding its adoption for radiological surveillance during childhood. Additionally, CTA fails to detect malignant transformation at an early stage and raises suspects of malignancy only when a cancerous mass has already formed. In addition, long-term surveillance is challenging in terms of high cost, patient compliance and transition of care with the involvement of adult thoracic surgeons and pulmonologists[80].

Box 2

Adults with CLM

Most congenital lung malformations (CLMs) are diagnosed during pregnancy. However, some remain undetected in the prenatal period and in childhood and are discovered in adulthood. An insight into the management of adults with CLM might give paediatric specialists a perspective on the possible future of children with CLMs managed conservatively.

Most adult patients with CLM (80%) complain about cough and respiratory infection as acute events or as recurrent symptoms throughout life; however, nearly 20% remain asymptomatic and the CLM is incidentally detected at screening imaging[149,151]. The presence of a CLM has been described in patients aged from 15 to 80 years. In all patients, chest radiography is performed as first-line imaging and, in all cases, can reveal an infection but fails to detect the CLM. Therefore, CT angiography is always performed to define the diagnosis and plan the surgery[151]. Adult thoracic surgeons recommend surgical resection as the treatment of choice in all adult patients with CLM, even in asymptomatic cases, as they are concerned about the susceptibility to infections and the risk of malignant transformation, which occurs in almost 10% of prenatally undiagnosed CLMs[149,151] and over 20% of prenatally undiagnosed congenital pulmonary airway malformation described in literature[149,151]. Conservative treatment is offered only when surgery is not feasible together with the recommendation of annual CT angiography to monitor the CLM.

Quality of life

So far, literature reviews on CLM outcomes have mainly focused on how the timing of lobectomy can enhance compensatory lung growth[154–156]. Modalities in diagnostics and surgical techniques have changed over time. The introduction of structural fetal ultrasonography, which has led to an increased antenatal detection rate[9] and intensive care treatment, has helped improve survival rates of neonates with severe respiratory problems, and minimal access surgery has gained popularity[124]. Thus, the data on long-term outcomes of children born in the past century can probably not be extrapolated to the cohort of neonates born with CLM during the past 10 years. To optimize postnatal management and parental counselling, an international multicentre registry is important and initiatives for such a registry are under way[156].

Uniform data on pulmonary morbidities are still lacking, especially data on general health, quality of life and societal participation. The focus of the currently available data is on general outcomes (such as physical growth), disease-specific outcomes (for example, respiratory tract infections, lung function and exercise tolerance) and treatment-related outcomes (such as musculoskeletal deformities).

Physical growth in infancy was found to be similar between infants who underwent surgical CLM resection and patients with non-resected asymptomatic CLM[157]. In a prospectively followed cohort of patients with resected CLM, weight-for-height was slightly below average at 2 years of age but within the normal range at 8 years of age[158,159].

Susceptibility to respiratory tract infections was studied in a population-based cohort, including 31 individuals with resected CLM that were born between 1991 and 2007 (ref. 160). Pneumonia and infections, including influenza, were more common in CLM-resected individuals than in the control cohort of 310 individuals of a population-based administrative data repository.

Small studies assessing lung function during infancy showed mild abnormalities in heterogeneous groups of patients with CLM, including reduced tidal volumes[161,162], reduced lung compliance[161] and increased airflow obstruction[157]. Interestingly, reduced lung compliance and airflow obstruction had also been reported in infants with CLM who did not undergo lung resection[157,161]. At school age, airflow obstruction mainly occurred in children who had undergone resection[158,163], although normal spirometry was reported in 76–86% of patients[164]. Exercise tolerance has been studied in only one group of 8-year-old participants in a structured longitudinal follow-up programme. Reduced exercise tolerance was observed in 40% of children who underwent resection and in 28% of the non-surgery group[158]. Lobectomy had been performed in most of the operated patients, although few patients underwent segmentectomy. The current results do not enable the drawing of any conclusion on the optimal surgical strategy for preservation of lung volumes, and functional MRI may be useful for further evaluation in the future[165]. Minimally invasive surgical techniques have more favourable outcomes than thoracotomies in terms of lung function[166] and development of musculoskeletal deformities[167,168].

International collaboration and registries for CLMs and the various treatment modalities, complications, and outcomes are important to determine the long-term quality of life of patients with CLM.

Outlook

There are ongoing advancements in the surgical treatment of CLMs. The thoracoscopic approach is already widely used[124]; however, future advances may focus on refining and expanding its application to further improve outcomes and reduce invasiveness. Moreover, personalized

surgical plans can optimize outcomes and minimize potential risks related to surgery. Integration of advanced imaging technologies, such as 3D imaging and printing, can provide detailed anatomical information for surgical planning. 3D-printed models of the affected lung segments can assist surgeons in pre-operative planning and intraoperative guidance, potentially improving surgical precision and outcomes.

A combination of virtual reality and augmented reality with emerging artificial intelligence algorithms has been explored for the pre-operative planning of pulmonary segmentectomy in adult patients[169]. In addition, a combination of virtual reality and artificial intelligence has also been used to preoperatively try to identify the exact vascular and bronchial anatomy and segmental borders in children with CLM[170]. However, although this approach could be used to remove gross disease, microscopic lesions might be left untreated, maintaining the risk of malignant transformation[19,171,172]. Unfortunately, current imaging modalities do not adequately distinguish between healthy and abnormal lung parenchyma, at least not at the microscopic level. Moreover, segmentectomy is burdened by a higher incidence of complications[131]. Thus, virtual reality-led and artificial intelligence-led anatomical segmentectomy could be considered as an approach only if gross disease seems to be limited to a single segment or in case of bilateral CLM.

Robotic surgery has been widely applied in adult patients, especially for urological and gynaecological surgeries but also in thoracic oncology[173]. The technical advantages over thoracoscopy include intuitive movements, more manipulative freedom and high-definition stereoscopic vision. Moreover, similarly to thoracoscopy, robotic surgery has been associated with shorter hospital stay, quick restart of daily activities and better cosmesis[173]. Although robotic surgery has been expanded to paediatric patients[174,175], its uptake in younger infants, especially for procedures in the thorax, has been slow due to technical challenges. The reduced chest space of infants would call for miniaturization of the devices and for a smaller distance between ports to decrease external cluttering[174,175]. So far, only a few series of paediatric robotic-assisted thoracic surgery have been reported[175,176], and even fewer infants with CLMs have undergone robotic-assisted lobectomy[177]. Until a dramatic miniaturization of the devices is reached, robotic-assisted thoracic surgery will not be an option for small infants.

Future efforts will likely focus on optimizing long-term outcomes for individuals with congenital lung malformations through standardized follow-up protocols, monitoring and research to understand the long-term effects of surgical interventions. Continued research, collaboration and integration of innovative technologies will shape the future of surgical treatment for CLMs, ultimately aiming to improve patient outcomes and quality of life. Moreover, genetic and biological studies should focus on addressing the potential trigger of malignant transformation of CLM and identify specific genetic mutations or alterations associated with such. Understanding the underlying genetic mechanisms can guide targeted therapies or early detection strategies.

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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[1]Paediatric Surgery, "F. Del Ponte" Hospital, ASST Settelaghi, Varese, Italy. [2]Department of Paediatric Surgery, Rocky Mountain Hospital for Children, Denver, CO, USA. [3]University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, UK. [4]Department of Paediatric Surgery and Intensive Care, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands. [5]Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong, China. [6]Department of Pathology and Clinical Bioinformatics, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands. [7]Departments of Radiology and Nuclear Medicine and Respiratory Medicine and Allergology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands. [8]Department of Radiology, University of Cagliari, Cagliari, Italy. [9]Department of Obstetrics and Gynecology, Fetal Medicine Unit, The Chaim Sheba Medical Center Tel-Hashomer, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. [10]Laboratory of Medical Genetics, Institute for Maternal and Child Health — IRCCS "Burlo Garofolo", Trieste, Italy. [11]Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy. [12]Department of Paediatric Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands.