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Congenital Pulmonary Airway Malformations in Children: Beyond the Pulmonary Cystic Lesion Is There Really an Associated Laryngo-Tracheal Abnormality?

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ABSTRACT

Background: Congenital pulmonary airway malformations (CPAMs) are rare developmental anomalies of the lower respiratory tract. Although their pulmonary and postnatal respiratory implications are well recognized, the possible coexistence of laryngotracheal abnormalities remains poorly investigated. Given the developmental continuity between the upper and lower airways, clarifying this relationship may have diagnostic, embryological, and clinical relevance.

Objective: To map the available evidence on laryngotracheal anomalies or dimensional alterations of the upper airway in patients with CPAM and to identify current knowledge gaps.

Methods: A scoping review was conducted according to Joanna Briggs Institute methodology and reported following PRISMA-ScR guidelines. PubMed, Scopus, and Web of Science were systematically searched without time restrictions, using terms related to CPAM, congenital lung malformations, laryngeal anomalies, tracheal anomalies, tracheomalacia, bronchomalacia, and prenatal or postnatal airway assessment. Studies reporting original data on pediatric patients with CPAM and associated laryngotracheal findings, imaging parameters, or relevant mechanistic evidence were included.

Results: The search identified 4,559 records. After duplicate and eligibility screening, six studies were included: two case reports, one case series, three original articles. The available evidence was limited and heterogeneous. Reported findings included tracheoesophageal fistula, tracheomalacia, and tracheobronchomalacia, mostly described incidentally. One case-control prenatal ultrasound study reported significantly smaller fetal upper airway dimensions in fetuses with congenital thoracic anomalies, including CPAM, compared with controls. Additional indirect evidence from fetal MRI and molecular studies suggested possible diagnostic and developmental overlap but did not establish a causal association.

Conclusions: Current evidence does not demonstrate a definitive association between CPAM and laryngotracheal anomalies. Existing data remain sparse, heterogeneous, and mainly hypothesis-generating. Future prospective studies using standardized prenatal and postnatal airway assessment, high-resolution imaging, endoscopy when clinically indicated, and molecular profiling are needed to clarify prevalence, mechanisms, and clinical relevance.

Giorgio Imbrogno and Lydia Alejandra Olaya Leon contributed equally and share second authorship.

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1 | Introduction

Congenital pulmonary airway malformations (CPAMs) are rare developmental anomalies of the lower respiratory tract, characterized by cystic and/or adenomatous lesions resulting from abnormal airway branching during fetal development [1, 2]. CPAM is a rare disease (1 in 10,000 to 1 in 35,000 births [3], however, it corresponds to the most frequent pulmonary malformation in children [1]. These malformations can lead to significant respiratory distress in neonates and are increasingly diagnosed prenatally due to advancements in imaging techniques [4, 5]. The prenatal detection of CPAMs allows for improved perinatal planning and management, potentially reducing morbidity and mortality associated with these lesions [1, 2]. The classification of CPAMs has evolved over time, with the Stocker classification system being widely adopted to categorize these lesions based on their histopathological features. Recent studies have revisited this classification, emphasizing the need for a nuanced understanding of CPAM subtypes to guide clinical decision-making [6]. Despite the benefits of prenatal diagnosis, the natural history of CPAMs remains variable [7]. Some lesions may regress spontaneously, while others can grow and cause mediastinal shift or hydrops fetalis. The decision to intervene prenatally or postnatally requires careful consideration of lesion size, growth rate, and associated complications [8]. Advancements in prenatal imaging, particularly fetal magnetic resonance imaging (MRI), have enhanced the ability to characterize CPAMs in utero. MRI provides detailed information about lesion composition, vascular supply, and relationship to adjacent structures, aiding in the differentiation of CPAMs from other thoracic anomalies [9]. A comprehensive approach that integrates imaging findings, clinical presentation, and histopathological features is essential for optimizing outcomes in affected infants [10]. Understanding the characteristics of CPAMs and of the surrounding structures is fundamental to increase our knowledge on this peculiar condition. Given the embryologic proximity between the developing tracheobronchial tree and lung parenchyma, it is plausible to hypothesize that aberrant lung development in CPAM may be associated with laryngotracheal anomalies. However, this potential correlation has not been systematically investigated. Therefore, the objective of this scoping review was to provide a comprehensive overview of the reported presence of laryngotracheal anomalies or dimensional alterations in patients with CPAM, while explicitly acknowledging the limited and heterogeneous nature of the available evidence [11]. Because the currently available evidence is limited and heterogeneous, a scoping review approach based on the Population–Concept–Context (PCC) framework was adopted to map the existing literature and identify potential knowledge gaps regarding the association between congenital pulmonary airway malformations and laryngo-tracheal anomalies.

2 | Materials and Methods

This scoping review was conducted in accordance with the methodology outlined by the Joanna Briggs Institute (JBI) for scoping reviews and was reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

A protocol for the review was developed prior to the commencement of the study. It defined the objectives, inclusion and exclusion criteria, search strategy, and methods for study selection and data extraction. Although the protocol was not registered on an open-access platform, it is available upon request from the corresponding author.

The review aimed to identify and synthesize existing evidence on the potential association between CPAM and anomalies of the upper airway, specifically focusing on the larynx and trachea. Studies were considered eligible if they involved pediatric patients with a confirmed diagnosis of CPAM and reported data relevant to laryngotracheal development, morphology, or pathology. Both structural anomalies (such as tracheomalacia or laryngeal atresia) and dimensional variations assessed through imaging or endoscopy were considered. We included all primary research designs reporting original data, including case reports, case series, cohort studies, case-control studies, and experimental studies using human or animal models. Review articles, editorials, commentaries, and expert opinions were excluded unless they presented unique data relevant to the research question. Only articles published in English were considered, and no time restrictions were applied to capture the widest possible body of evidence.

The review question was structured according to the PCC framework recommended for scoping reviews. The population included pediatric patients diagnosed with CPAM. The concept explored was the potential presence of associated laryngotracheal anomalies or dimensional alterations of the upper airway. The context focused on congenital airway development and the related diagnostic and clinical implications in prenatal and postnatal settings.

To ensure comprehensive coverage of the literature, we conducted a systematic search of three major electronic databases: MEDLINE (via PubMed), Scopus, and Web of Science. To reduce the risk of missing relevant studies, the search strategy combined controlled vocabulary and free-text terms related to congenital pulmonary airway malformation and broader congenital lung malformations, as well as terms related to laryngotracheal abnormalities, tracheal anomaly, laryngeal anomaly, tracheomalacia, bronchomalacia, airway obstruction, bronchoscopy, fetal MRI, prenatal ultrasonography, and congenital high airway obstruction sequence. After rechecking the expanded strategy, no additional studies directly fulfilling the inclusion criteria were identified. The final search was completed in 05/2025. In addition to database searching, we screened gray literature sources and the reference lists of included articles to identify any further relevant studies.

All references were imported into citation management software, and duplicates were removed. Two independent reviewers (LAOL and GI) screened titles and abstracts for relevance. Studies considered potentially eligible were retrieved in full text and independently assessed for eligibility by the same two reviewers according to the predefined inclusion criteria. Any disagreements were resolved through discussion or, if necessary, by consulting a third reviewer (AB). The reasons for the exclusion of full-text articles were recorded to ensure transparency.

Data from the included studies were extracted using a standardized charting form, which was piloted and refined during the initial phase of the review. The extracted data included bibliographic information, study design, country of origin, patient demographics, type and classification of CPAM, description of any associated laryngotracheal anomaly, diagnostic modalities employed (such as ultrasonography, CT, MRI, or endoscopy), and clinical or histopathological findings. When available, information regarding pathophysiological or embryological mechanisms was also recorded. Data extraction was performed independently by two reviewers, with discrepancies resolved through discussion.

Given the expected heterogeneity of study designs, populations, and outcome measures, a narrative synthesis approach was adopted. The results are presented descriptively, with summary tables used to illustrate the characteristics of included studies and highlight patterns in the types of laryngotracheal anomalies reported. In line with the JBI methodology for scoping reviews, no formal assessment of the risk of bias or methodological quality was conducted, as the primary aim of the review was to map the extent and nature of existing evidence rather than to perform a critical appraisal or meta-analysis.

3 | Results

The bibliographic search yielded a total of 1863 records in PubMed, 996 in Web of Science, and 1700 in Scopus, using the combined keywords "Congenital Pulmonary Airway Malformation," "CPAM," "larynx anomaly," and "tracheal anomaly." After merging the results and removing duplicates, 1536 unique articles were retained for title screening. Of these, 297 were considered potentially relevant based on title and proceeded to abstract review. Following abstract evaluation, six studies met the inclusion criteria and were selected for full-text analysis. These consisted of two case reports, one case series, and three original articles (PRISMA Flow Diagram, Figure 1).

Given the heterogeneity of the included literature, the studies were not interpreted as providing equivalent levels of evidence. Instead, they were stratified according to their main contribution to the review question. Three studies provided direct but anecdotal clinical evidence, including two case reports and one small case series describing the coexistence of CPAM with tracheoesophageal fistula, tracheomalacia, or tracheobronchomalacia. One observational case-control study provided prenatal imaging evidence by assessing fetal upper airway dimensions in fetuses with congenital thoracic anomalies. One retrospective imaging study contributed differential-diagnostic evidence by highlighting the role of fetal MRI in distinguishing CPAM-like thoracic findings from congenital high airway obstruction sequence. Finally, one experimental study provided indirect mechanistic evidence regarding pathways involved in tracheal chondrogenesis and CPAM development.

The included literature provided limited but noteworthy data on the potential coexistence of laryngotracheal anomalies in patients with CPAM. As summarized in Table 1, most of the available evidence comes from case-based reports, where upper airway anomalies are often described as incidental findings rather than primary endpoints of investigation. Specifically, one case reported an association between CPAM and tracheoesophageal fistula [13], another described extensive tracheomalacia involving the entire lung [14], and a third documented combined tracheomalacia and bronchomalacia secondary to extrinsic vascular compression from the aortic arch and right pulmonary artery [12].

Among the selected studies, the work by Song et al. [16] was the only observational case-control study that systematically evaluated fetal upper airway anatomy in the context of congenital thoracic anomalies. Using prenatal ultrasonography, the authors measured tracheal width, the narrowest segment of the airway, and subglottic and vestibular laryngeal dimensions in fetuses with CPAM, bronchopulmonary sequestration (BPS), or congenital diaphragmatic hernia (CDH), and compared these values with those of healthy controls. A total of 41 fetuses with thoracic anomalies (22 with CPAM) and 127 controls were assessed. The study demonstrated significantly smaller airway dimensions in fetuses with congenital thoracic anomalies compared with controls. For example, at 20–24 weeks of gestation, the mean tracheal width was 2.608 ± 0.320 mm in controls versus 1.786 ± 0.313 mm in cases, while the subglottic cavity width measured 1.839 ± 0.240 mm in controls versus 1.386 ± 0.228 mm in cases. Similar differences were observed for the narrowest lumen width and the laryngeal vestibule width, which were consistently smaller in fetuses with congenital thoracic anomalies. These findings suggest a potential role for upper airway measurements as adjunctive parameters in the prenatal diagnosis of congenital intrathoracic lesions.

The other two original studies were retained as indirect, non-equivalent evidence: Zeng et al. contributed mechanistic data on tracheal chondrogenesis and CPAM development, whereas Guimaraes et al. contributed differential-diagnostic information on fetal MRI features that may distinguish CPAM-like thoracic findings from congenital high airway obstruction sequence [15, 17]. These studies should not be interpreted as direct proof of a clinical association between CPAM and laryngotracheal anomalies.

4 | Discussion

The available literature on the association between laryngotracheal anomalies and CPAM, or more broadly with pulmonary malformations, remains extremely limited and fragmented. This finding itself represents one of the main outcomes of the present scoping review, whose purpose was to map the currently available evidence and identify existing knowledge gaps in this field. The presence of tracheoesophageal fistulas and tracheo-bronchomalacia associated with vascular anomalies is reported only anecdotally in case reports, which tend to focus primarily on the diagnostic and therapeutic aspects of CPAM rather than upper airway abnormalities. Even in the case series on giant CPAM, the presence of tracheomalacia in one out of three enrolled patients appears more likely to be incidental rather than a consistent association. The predominance of isolated case reports and small case series highlights the absence of systematic investigations specifically addressing this potential

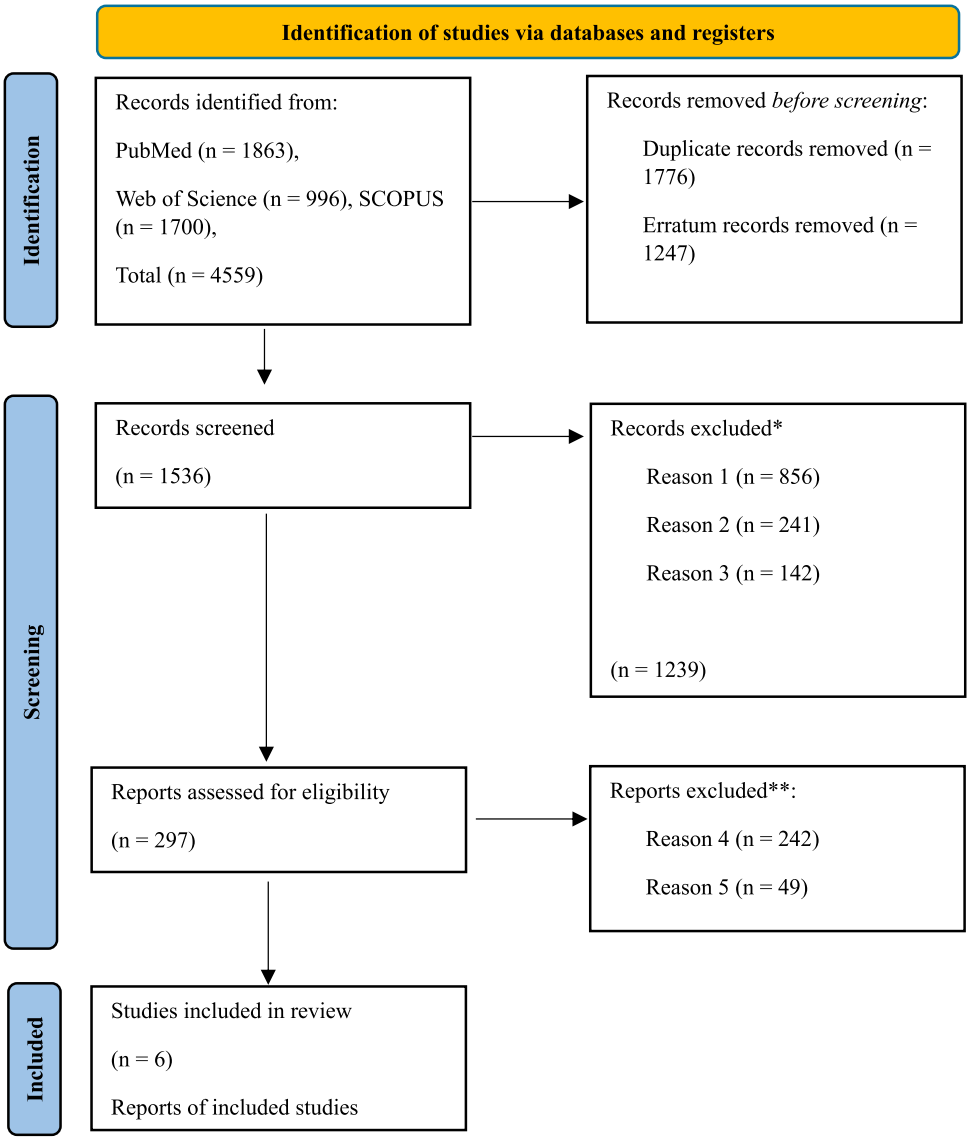


FIGURE 1 | Literature search flow diagram with keywords including congenital pulmonary airway malformation," "CPAM," "larynx anomaly," and "tracheal anomaly." *Reason 1: Topic, Reason 2: Review, Reason 3: Language other than English, Reason 4: Not focused on laryngotracheal anomalies, Reason 5: Not original article or duplicates. [Color figure can be viewed at wileyonlinelibrary.com]

association. This observation further supports the need for structured prospective studies evaluating the upper airway in patients with congenital pulmonary airway malformations.

The included studies are highly heterogeneous in design, population, aims, and diagnostic approach. Therefore, the available literature cannot be interpreted as a homogeneous body of evidence supporting a definite association between CPAM and laryngotracheal anomalies. Rather, it represents a fragmented collection of clinical observations, prenatal imaging findings, differential diagnostic considerations, and experimental data that together identify a possible but unproven area of developmental and clinical overlap.

In this context, no systematic correlation between CPAM and tracheal anomalies appears evident, and it can be considered that the upper and lower airways form from different embryological structures, respectively the pharyngeal arches and the respiratory diverticulum of the primitive gut. However, the upper and lower airways develop concurrently during embryological development and these two processes are intricately linked, as the development of the lower airways relies on the proper formation of the upper airway structures, to guarantees proper clearance of lung fluids [15, 18].

Following this idea, the study by Song et al. stands out, as it focuses specifically on the measurement and comparison of laryngeal and tracheal dimensions in healthy fetuses and those affected by pulmonary malformations (including CPAM). This study demonstrated that the measured parameters were significantly smaller in fetuses with pulmonary malformations, leading the authors to suggest that these measurements may offer potential diagnostic clues for congenital intrathoracic lesions.

In the work by Song et al., although the dimensions were significantly different, the authors did not report (as it was beyond the scope of their study) whether these reduced dimensions were associated with postnatal symptoms.

TABLE 1 | The table summarizes the main findings from the literature review on the association between CPAM and laryngotracheal anomalies.

Article	Type of study	Laryngotracheal anomalies	Main diagnostic technique	Aims
Baird et al. (2016) [12]	Case report	Tracheo-bronchomalacia	Bronchoscopy + CT angiogram	Description of the clinical case
Fijasri et al. (2023) [13]	Case report + review	Tracheoesophageal fistula + esophageal atresia	X-ray + Chest CT	Description of the clinical case
Ben-Ishay et al. (2012) [14]	Case series	Tracheomalacia	X-Ray, US, MRI	Consideration on pneumonectomy in multilobular giant CPAM
Guimaraes et al. (2009) [15]	Retrospective observational study	/	1.5 T MRI with SSFSE sequences	Describe radiological patterns, identify level of obstruction, differentiate CHAOS from other pulmonary alterations, and evaluate correlation with postnatal outcomes
Song et al. (2023) [16]	Observational case-control study	Reduced overall tracheal dimension	US	To compare fetal upper airway parameters between normal foetuses and foetuses with intrathoracic lesions, and to try to verify its diagnostic value in intrathoracic lesions
Zeng et al. (2023) [17]	Experimental preclinical study	/	RNA sequencing, in vitro cell culture, cell function testing, molecular analysis	To clarify the functional role of the miR548au3p/CA12 axis in tracheal chondrocyte proliferation and differentiation, and to suggest a possible pathogenetic mechanism in CPAM

Abbreviations: CHAOS, Congenital High Airway Obstruction Syndrome; CPAM, Congenital Pulmonary Airway Malformation; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; US, Ultrasonography; TOF, Tracheoesophageal Fistula.

Another useful imaging modality for assessing fetal upper airway dimensions is MRI, as demonstrated by Guimaraes et al. in their study of fetuses affected by Congenital High Airway Obstruction Sequence (CHAOS), a rare clinical condition characterized by obstruction at the laryngotracheal level and consequent distal airway dilatation, accompanied by multiple pulmonary anomalies. Particularly noteworthy is that some fetuses initially suspected to have CPAM based on ultrasound findings were subsequently reclassified as CHAOS following upper airway MRI evaluation. In fact, MRI showed an abnormally dilated airway distal to the level of obstruction in all cases—findings that are not easily identified via ultrasound. Differentiating between these two conditions is clinically relevant, as CHAOS typically requires intrauterine interventions or planned delivery via ex utero intrapartum treatment (EXIT) to tracheostomy [15].

Zeng et al. provided indirect mechanistic evidence by investigating miRNA expression profiles in patients with CPAM and the effects of miR-548au-3p in rat tracheal chondrocytes [17]. The authors reported that miR-548au-3p modulates markers involved in chondrocyte proliferation and extracellular-matrix remodeling, supporting a possible role in tracheal chondrogenesis and CPAM development. However, because these data derive from experimental models and do not demonstrate laryngotracheal anomalies in patients with CPAM, they should be interpreted as mechanistic and hypothesis-generating rather than as direct clinical evidence of association.

Several key transcription factors and signaling molecules that orchestrate normal lung development, such as NKX2-1, SOX2, SOX9, FGF10, TBX4/5, SHH, BMP4, and WNT, are also expressed and functionally active during tracheal morphogenesis [10, 19, 20]. This overlap highlights the existence of shared molecular pathways that guide the coordinated development of the trachea, bronchi, and lungs from their common embryonic origin, the anterior foregut. Such developmental continuity suggests that early disturbances in these signaling networks could, in principle, affect multiple components of the respiratory tract.

Nevertheless, the molecular alterations identified in congenital pulmonary airway malformation (CPAM) differ substantially from those typically associated with congenital tracheal anomalies. CPAMs are frequently characterized by somatic mosaic mutations within the RAS–MAPK signaling cascade, particularly involving the KRAS gene [21–23]. These alterations appear to drive localized epithelial proliferation and aberrant airway patterning rather than global morphogenetic disruption.

In contrast, congenital tracheal malformations—including tracheal agenesis, congenital stenosis, complete tracheal rings, and tracheoesophageal fistula—are most often linked to defects in foregut and tracheal differentiation pathways. Experimental and genetic evidence implicates dysregulation of transcriptional regulators and morphogens such as NKX2-1, SOX2, TBX4/TBX5, BMP, SHH, WNT, NOGGIN, and components of the retinoic acid signaling system, as well as copy-number variants in syndromic contexts [6, 24–26].

Taken together, current data do not support a direct genetic continuum between CPAM and tracheal malformations. Rather, these entities appear to represent distinct developmental disturbances: CPAM arising from somatic oncogenic mosaicism affecting airway epithelium, and tracheal malformations resulting from germline or early embryonic patterning defects within the foregut–tracheal domain [10, 21, 24]. Despite this mechanistic divergence, both conditions underscore the crucial developmental interdependence of the trachea and lung, which share a common embryological progenitor and rely on overlapping molecular frameworks for their proper formation.

A key unresolved issue is whether the coexistence of CPAM and laryngotracheal findings reflects a primary developmental association, a secondary phenomenon, or an incidental coexistence. The currently available literature does not allow this distinction to be made with confidence. Case reports describing tracheoesophageal fistula, tracheomalacia, or tracheobronchomalacia may represent coincidental associations, particularly in complex congenital phenotypes. In other cases, airway narrowing or malacia may be secondary to mechanical factors, including mass effect, mediastinal shift, vascular compression, or altered fetal lung mechanics. Conversely, prenatal imaging data showing reduced upper airway dimensions and experimental data implicating pathways involved in tracheal chondrogenesis raise the possibility of a shared developmental vulnerability. Therefore, the present evidence should be interpreted as hypothesis-generating only and not as proof of a causal, systematic, or primary developmental association.

Defining an association between CPAM and laryngotracheal anomalies could also have significant clinical implications. First, the presence of tracheobronchial anomalies, particularly those involving airway narrowing, may increase the difficulty of intubation and extubation in pediatric patients [27], a factor that must be carefully considered during surgical planning. Moreover, the presence of tracheobronchial anomalies appears to be generally associated, in the broader population, with a higher risk of hospitalization, comorbidities, and even in-hospital mortality. This risk also seems to increase in cases of late diagnosis compared to early detection [28]. The strict connection between nearby structures can justify even the subtle structural and functional alterations that can involve the contiguous airways, even in cases where the malformation appears localized. Farolfi et al. [29] reported a measurable lung function impairment in approximately one-fifth of their cohort. Importantly, the authors noted that such sequelae persisted even in children who were asymptomatic before surgery, indicating that the developmental anomaly may have broader physiological consequences than those directly addressed by surgical excision. These findings support the hypothesis that both the malformation itself and the resection procedure can modify airway geometry, disrupt normal lung–tracheal coupling, and impair compensatory growth of the remaining parenchyma. Moreover, the persistence of inflammation and bronchial hyperreactivity suggests long-term alterations in airway dynamics, underscoring that surgical correction does not fully normalize respiratory function. Taken together, these observations support the need to evaluate respiratory outcomes in the context of the whole airway-lung system, but they do not prove that CPAM and laryngotracheal anomalies share a single causal mechanism.

Overall, current evidence should be regarded as exploratory. It may justify careful prenatal and postnatal attention to the airway in selected patients and provides a rationale for prospective research, but it does not support routine inference of a causal or systematic laryngotracheal abnormality in all patients with CPAM.

Several limitations must be emphasized. First, the number of included studies was very small, reflecting the scarcity of literature specifically addressing laryngotracheal findings in patients with CPAM. Second, most available data derive from case reports or small case series, in which upper airway anomalies were usually reported incidentally rather than assessed as predefined outcomes. Third, the included studies used different diagnostic modalities and focused on different clinical or developmental questions, limiting comparability. Fourth, no standardized protocol for airway assessment was reported across the included literature. For these reasons, the present review cannot estimate the prevalence of laryngotracheal anomalies in CPAM, quantify the risk of association, or establish causality. Its contribution should therefore be interpreted as exploratory and hypothesis-generating.

5 | Conclusion

This scoping review highlights the paucity, heterogeneity, and fragmentation of the available evidence regarding laryngotracheal findings in patients with CPAM. The current literature does not allow a definitive association to be established, nor does it permit distinction between primary developmental abnormalities, secondary airway effects, and incidental coexistence. Therefore, the findings of this review should be interpreted as exploratory and hypothesis-generating. Nevertheless, the limited available evidence suggests that this under-investigated topic may have clinical relevance for prenatal assessment, perinatal airway planning, and postnatal follow-up. Future prospective studies should adopt standardized airway evaluation protocols, integrate prenatal and postnatal imaging, and explore developmental and molecular mechanisms to better define the prevalence, pathogenesis, and clinical impact of laryngotracheal anomalies in this population.

Author Contributions

Antonio Mario Bulfamante: conceptualization, investigation, writing – original draft, writing – review and editing. **Ugo Maria Pierucci:** investigation, writing – original draft, writing – review and editing, supervision. **Giorgio Imbrogno:** Investigation. **Lydia Alejandra Olaya Leon:** Investigation. **Gloria Pelizzo:** writing – review and editing, supervision, conceptualization. All listed authors contributed substantially to this manuscript and approved the final submitted version.

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Conflicts of Interest

The authors declare no conflicts of interest.

AI Statement

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

Data Availability Statement

Data reported in this study are available upon request from the Corresponding Author.

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