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# ASSOCIATION OF ACID REFLUX AND LARYNGOMALACIA : A COMPREHENSIVE SYSTEMATIC REVIEW

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## ABSTRACT

***Background:*** *Laryngomalacia (LM) is a common cause of stridor in infants and young children. It is characterized by reflux episodes that are slightly acidic, which harm the supraglottic tissues and exacerbate airway collapse. Further investigation is required to ascertain the presence of the gastric proteolytic enzyme pepsin in the oral secretions of patients with less severe LM, as it has been proposed as a biomarker for both weakly acidic and nonacid reflux events.*

***Methods:*** *This systematic review focused on full-text English literature published between 2014 and 2024, adhering to PRISMA 2020 principles. Without a DOI, editorials and review papers that were published in the same journal as the submission were not accepted. ScienceDirect, PubMed, and SagePub were only a few of the web resources used to compile the literature.*

***Result:*** *Following a thorough screening process consisting of three stages, six papers were determined to have pertinent connections to our ongoing comprehensive investigation. Following that, the text as a whole was thoroughly studied and these sections received more attention.*

***Conclusion:*** *Recent research has revealed a link between laryngomalacia (LM) and pepsin, a diagnostic marker, but no significant differences have been found. Pepsin is a common comorbidity in LM patients and serves as a biomarker for airway reflux, but its harmful impact on proximal airways remains unclear.*

**Keyword:** *Laryngomalacia, reflux, pepsin, acidic, biomarker*

## INTRODUCTION

Laryngomalacia (LM) is the most common cause of stridor in newborns and children, accounting for 60% to 70% of cases.[1,2] It is characterized by the collapse of supraglottic tissues during inspiration.[1] The pediatric otolaryngology literature has given laryngomalacia a great deal of attention as one of the disorders of the upper airway that children are diagnosed with most frequently.[3] Stridor usually appears in the first few weeks of life and can worsen as the baby becomes more active over the first four to eight months of life. Mild to moderate LM usually goes away on its own by the time the infant is 24 months old. However, severe LM affects 4% to 20% of patients and may cause symptoms such as obstruction of the airway, failure to grow, or pectus excavatum. In such cases, supraglottoplasty surgery may be necessary.[4]

Research indicates that laryngopharyngeal reflux (LPR) may contribute to the pathophysiology and/or severity of LM. Reflux occurs in 65% to 100% of babies with LM, and it can damage or weaken supraglottic tissues, leading to or worsening the collapse during inspiration.[5] It has been shown that breathing against an obstruction in the airway, as in LM, results in higher negative intrathoracic pressures and a higher probability of passing through the esophageal sphincters' antireflux barrier. Consequently, it has been hypothesized that LPR episodes, which cause edema and inflammation of the laryngeal tissues, will exacerbate airway collapse in LM.[2] Since the refluxate often reaches the laryngopharynx weakly acidic or nonacidic, LPR is a diagnostic challenge that is challenging to identify using conventional techniques. The gold standard for diagnosing nonacid reflux events using pH is multichannel intraluminal impedance (MII-pH) monitoring, yet it is highly invasive and unsuitable for use in young populations.[5]

Due to the mucosa's ability to buffer refluxate as it passes through, reflux events that reach the laryngopharynx are typically mildly acidic or nonacidic. This type of reflux has been linked to laryngeal symptoms and signs. For this reason, pH probe testing is a subpar diagnostic method for LPR. Because pepsin, a gastric proteolytic enzyme mostly produced in the stomach, is found in refluxates of all pH values, it can be used as a biomarker for both weakly acidic and nonacid reflux.[6] Various clinical and surgical specimens can be identified by biochemical analysis, which has been used to show the relationship between pepsin and aerodigestive tract illnesses such as chronic rhinosinusitis, otitis media, broncho-pulmonary dysplasia, and LPR disease. Pepsin has also been found in the laryngopharynx, trachea, lung, sinus, middle ear, combined sputum, saliva, and exhaled breath condensate. Enzyme-linked immunosorbent assays (ELISA), which are reasonably priced and enable medium- to high-throughput specimen examination, are examples of pepsin tests. As far as we are aware, no reports of laryngeal pepsin in children with severe LM exist.[2]

Recent research indicates that a diagnostic tool for low-proton reflux occurrences may be the stomach enzyme pepsin. Pepsin has been proposed as a biomarker for weakly acidic and nonacidic reflux episodes because it is present in refluxate regardless of pH.[7] According to research, pepsin has a diagnostic significance in cases of severe lipomatosis (LM) because it is found in the supraglottic lavage specimens of 80% of patients with LM who need surgical intervention and 0% of controls without LM.[2] To be more broadly applicable, this finding needs to be further investigated as it is restricted to a severe subset of LM patients.[5] In pediatric settings, salivary pepsin measurement has previously been associated with objective evidence of reflux events,[8] but there is little information about its presence in the oral secretions of children with less severe LM.[5] Research has demonstrated that subjecting hypopharyngeal tissues to pepsin at pH 7 in vitro stimulates the release of cytokines, including IL-1β and IL-8, suggesting a possible involvement of these cytokines in reflux-induced inflammatory alterations. It is thought that IL-1β and IL-8 act as reflux esophagitis mediators. Although studies on IL-1β and IL-8 levels in saliva have been done, nothing is known about their presence in the oral secretions of children with LM and LPR.[5]

This study aims to provide a comprehensive overview of the literature released over the last ten years regarding the association of acid reflux and laryngomalacia.

## METHODS

### Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were carefully followed by the research's author. This was to make sure the study complied with all regulations. The selected methodology was meticulously crafted to guarantee the precision and coherence of the research outcomes.

## CRITERIA FOR ELIGIBILITY

The research conducted over the previous ten years on the impact of congenital heart disease on brain development and neurodevelopmental outcomes is thoroughly reviewed in this article. This study uses a comprehensive data analysis to try to explain and enhance patient treatment procedures. This thesis' main goal is to highlight the significance of noteworthy topics found in a range of literary works.

In order to ensure the accuracy of the data utilized in this study, specific inclusion and exclusion standards were put in place. Items must have been published in English between 2014 and 2024 in order to be eligible for inclusion. Among the exclusion criteria are editorials, submissions without a DOI, published reviews, and duplicate journal entries.

## SEARCH STRATEGY

The study's keywords include "Association of Acid Reflux and Laryngomalacia". For this research, the following Boolean MeSH keywords were entered into the databases: ((“acid reflux”[MeSH Terms] OR (“acid reflux“[All Fields] AND “laryngomalacia”[All Fields]) OR (“laryngomalacia”[MeSH Terms] OR (“laryngomalacia”[All Fields] AND “acid”[All Fields]) AND (“association”[MeSH Terms] OR “association”[All Fields] OR “effect”[All Fields] OR “correlation”[MeSH Subheading] OR “correlation”[All Fields] OR “result”[All Fields])).

## DATA RETRIEVAL

The authors carefully examined the abstract and title of each publication to determine its importance before starting this systematic investigation. Only papers that met the inclusion criteria and endorsed the goals of the article were given additional consideration. In the end, a consistent pattern identified through several inquiries produced a definitive answer. Entries in full text only in English were accepted. Content that satisfied all planned inclusion criteria and had a clear connection to the study's topic matter was produced using the strictest screening methodology. Research that did not fit these patterns was typically disregarded and their conclusions were overlooked. Numerous items, including titles, authors, publication dates, places, study methodologies, and variables, were found and reviewed during the assessment.

## QUALITY ASSESSMENT AND DATA SYNTHESIS

The authors separately assessed the research included in each article's title and abstract in order to determine which papers require further investigation. Examining every document that satisfied the requirements set down in advance for review inclusion was the next step. The papers that made up the review were chosen based on the evaluation results. This criterion expedited the selection of publications for subsequent research, allowing for a thorough evaluation of previous studies and the criteria that qualified them for the review.

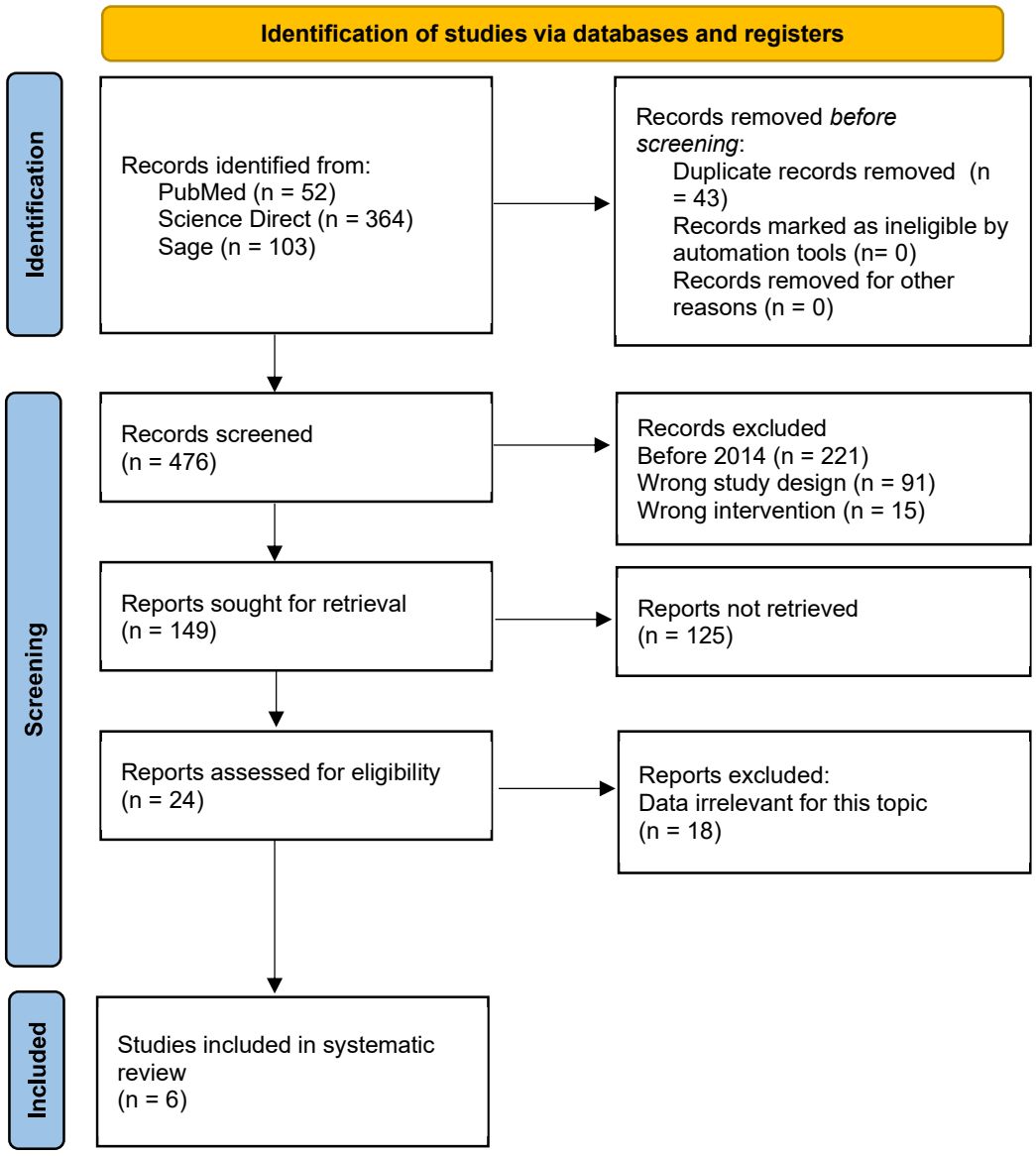


**Figure 1. Article search flow chart**

## RESULT

Initially, more than 400 publications were collected by our study team from reliable sources like Science Direct, PubMed, and SagePub. Only six papers were found to be directly relevant to our ongoing systematic examination after a rigorous three-level screening process. After that, these passages were chosen for more study and a careful reading of the complete work. For convenience of viewing, the evaluated material for this analysis is compiled in Table 1.

**Table 1. The literature included in this study**

| Author | Origin | Method | Sample | Result |
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| **Isaac et al.[9] (2016)** | Canada | Systematic Review | 3 studies | Three publications (n = 411 patients) out of 1146 that were found to satisfy the inclusion and exclusion criteria. With stridor resolution serving as the sole endpoint, all were retroactive. The time to resolution varied from 4 to 42 months, with an 89% resolution rate. Studies lacked objective endpoints and a |

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| | | | | follow-up, and the level of evidence was poor. No meta-analysis could be done. |
| **Calvo-Henriquez et al.[7] (2017)** | Spain | Systematic Review | 12 studies | There were twelve studies in total. Except for two, every study that was included discovered statistically significant differences in pepsin levels between cases and healthy controls. |
| **Luebke et al.[2] (2017)** | USA | Randomized Controlled Trial | 15 patients | Five control participants and ten laryngomalacia subjects were included. Patients with laryngomalacia (8/10) had pepsin in their lavages; controls (0/5; P 5.007) did not have any. In lavages (8/10) compared to biopsies (4/10; P 5.046) of laryngomalacia patients, pepsin was found more frequently. In comparison to control lavages, a higher median pepsin concentration was seen in cases of laryngomalacia (P 5.025). |
| **Klimara et al.[5] (2019)** | USA | Randomized Controlled Trial | 32 patients | Sixteen individuals with laryngomalacia and sixteen controls participated in the study. Pepsin was detected in the oral secretions of patients with laryngomalacia (13/16) more frequently than in the controls (2/16). Supraglottoplasty was necessary for four laryngomalacia patients because of their symptoms. The levels and presence of salivary pepsin did not significantly correlate with the need for surgical management, nor did the presence or levels of IL-1β or IL-8 significantly correlate with the diagnosis of laryngomalacia or the need for surgical management. |
| **Jaffal et al.[10] (2020)** | Canada | Systematic Review | 4 studies | In the search, 512 abstracts were located. The four studies that met the selection criteria included 425 young children as their subjects. Three studies were uncontrolled case series, while one was a planned cohort study. Every study, other than one, evaluated patients' swallowing with a specific instrument when they showed clinical indications of |

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| | | | | a swallowing issue. The total estimated (range) prevalence of SwD was 49% (13.9–90.6%). |
| **Duncan et al.[11] (2021)** | USA | Retrospective Study | 236 patients | The analysis included 236 people in total, with a mean age of 62.6 ~ 4 days; medication for acid suppression was received by 55% of the patients. Even after accounting for confounding variables, acid suppression participants had a higher probability of hospitalization for respiratory problems, were more likely to have supraglottoplasty, and had a shorter time to surgery (5.64 ~ 0.92 vs 7.98 ~ 1.92 months). Thickened patients had a longer time to supraglottoplasty (9.3 ~ 1.7 vs 4.56 ~ 0.73 months) and fewer respiratory inpatient nights even after the correction. |

Three retrospective cohort studies by Isaac et al. on LM, each involving 58-233 patients, used flexible fiberoptic laryngeal endoscopy (FFLE) to diagnose Laryngomalacia (LM). The proportion of patients lost to follow-up was not specified. All three studies used stridor resolution as the primary outcome, with no objective endpoints. The resolution time ranged from four to 42 months. Methodological issues, such as unclear recruitment criteria and follow-up completion, hindered meta-analysis. Despite these limitations, the studies had low selection bias and generalizable results.[9]

The study by Calvo-Henriquez et al. found statistically significant differences in pepsin concentration in patients with Laryngomalacia symptoms compared to healthy controls. The study found higher levels of pepsin in patients upon waking, emphasizing the importance of taking samples upon waking. However, there is controversy about the presence of pepsin in healthy controls. The study also found that pepsin was present in biopsies taken from awakened patients, with a sensitivity of 80% and a specificity of 85.7%.[7]

In their investigation, Luebke et al. discovered that patients with severe LM had higher pepsin detection rates than control patients. Pepsin concentration in LM lavages was found to be substantially greater than in control lavages, according to the results. Additionally, the study did not discover any connection between the LM group's pepsin content or presence.[2]

Patients with LM and controls without stridor, LM, or airway obstruction were examined in the study by Klimara et al. The mean age differed significantly, however there was no discernible variation in terms of gender or race. Patients with LM had higher rates of pepsin detection, but there was no discernible change in the requirement for surgery. Pepsin levels did not significantly correlate with the requirement for surgery.[5]

In the Jaffal et al. study, pediatric otolaryngologists and speech-language pathologists evaluated kids with LM in four tertiary care center studies. The patients with severe LM or those exhibiting symptoms suggestive of swallowing dysfunction (SwD) had their swallowing abilities evaluated using these devices. Patients with preterm and gastroesophageal reflux disease (GERD) were included in the research, which varied widely in terms of age groupings. 279 patients had their LM severity classified, and there was no discernible variation in the results of objective swallowing tests depending on the degree of LM.[10]

According to Duncan et al., there was no discernible variation in the severity categories of laryngomalacia patients receiving acid suppression treatment based on the seniority of their otolaryngologist or airway clinic. On the other hand, 55% of participants employed acid suppression, with 27% using H2 receptor antagonists (H2RA), 11% receiving proton pump inhibitors (PPIs), and 17% receiving both. Individuals undergoing acid suppression had a twofold increased risk of respiratory hospitalization and a higher number of hospitalization nights. Treatment for acid suppression raises the chance of supraglottoplasty, particularly in moderate-to-severe illness.[11]

## DISCUSSION

Recent literature on laryngomalacia (LM) has shown significant interest in the outcomes of surgical treatment for the disease. However, there is a lack of evidence on the natural history of LM, particularly in terms of spontaneous resolution.[9] Only three studies adequately reported on the rate and time to spontaneous resolution, with the evidence-based on level IV studies with relatively few patients. The evidence on the spontaneous resolution of LM symptoms is subjective and lacks objective or standardized endpoints. Prospective longitudinal studies with adequate follow-up are needed to answer important clinical questions about LM's natural history. Studies have identified new entities such as late-onset, exercise-induced, and occult LM, making objective endoscopic assessment crucial. No studies have documented all symptoms at presentation and resolution, and even in surgical outcomes, symptoms and signs of snoring/sleep-disordered breathing (SDB) and swallowing dysfunction (SD) were not addressed.[9]

Studies have found a relationship between LPR and pepsin, a reliable diagnostic marker.[12] However, no significant differences were found between LPR and pepsin, possibly due to the use of reflux symptom index (RSI) for patient selection and not specifying the time of day for saliva sample taking.[13] Recent studies have found no statistically significant differences positive rates of pepsin tests between patients with and without typical reflux symptoms. Studies found pepsin in healthy controls, but at a lesser concentration than in patients. There is variability in the cutoff point to consider pepsin as pathologic, and there is no consensus on the use of nonquantitative tests like Peptest. Questions remain about the diagnosis of LPR with only one positive sample. The diagnostic tool used in these studies is the Peptest commercial kit, which is more sensitive and aggressive than saliva/sputum tests. Further research is needed to compare Peptest with biopsies to determine the best method for LPR diagnosis.[7]

The study by Klimara et al. aimed to understand the role of salivary pepsin in gastrointestinal reflux disease, specifically laryngomalacia, by analyzing its presence and level in oral secretions.[5] Patients with LM often have pepsin, a biomarker for reflux in the airways, as a comorbidity. A pilot study looked at the presence and content of pepsin in supraglottic tissue and lavage samples to determine the incidence of LPR in LM patients. The findings showed that there was a higher frequency of pepsin detection in lavage samples, suggesting a higher sensitivity for identifying proximal reflux. In line with reports of LM accompanied by reflux and earlier research demonstrating the presence of pepsin in supraglottic lavage in 80% of individuals with severe LM necessitating supraglottoplasty.[2] However, the role of pepsin in LM patients was not statistically significant. Control patients had lower levels of pepsin, suggesting higher reflux volumes in LM patients.[5] However, research has shown the harmful effects of pepsin on proximal airways in LM patients.[2] Acid-targeting antireflux medications have shown questionable benefits,[14] suggesting refluxed gastric acid may not play a role in LM pathophysiology. Nissen fundoplication supports a causal role for nonacid reflux components in LM. Further study is warranted to understand pepsin's contribution to LM pathophysiology. The study focuses on diagnosing reflux in patients with LM using pepsin but found no correlation between pepsin concentration and disease outcomes or severity.[2]

Salivary IL-1β or IL-8 levels did not significantly correlate with other outcomes or measurements, such as pepsin in the LM group or the control group, according to Samuel & Johnston's study.[6] To make more definitive findings, more studies comparing salivary pepsin, IL-1β, and IL-8 levels to more reliable methods like MII-pH monitoring are required.[5] LM, also known as gastrointestinal reflux disease, is distinguished, even in cases of nonacid reflux, by inflammation in the proximal airway tissue.[6] Patients with LM may experience stridor due to gastric acid pepsin, which has been connected to inflammatory diseases. Nevertheless, there is scant data to support the use of anti-reflux drugs to treat LM symptoms, particularly in those who also have concomitant GERD.[15] This implies that the pathophysiology of LM may include gastric acid to a limited extent, but it does not rule out the possibility that non-acid stomach contents, such as pepsin, may play a pathophysiologic role in the illness, as they may in other upper respiratory disorders.[5] A few of the study's shortcomings are the difference in mean age between the LM and control groups and the uncertainty around the optimal time to collect data to detect extra-esophageal reflux.[5,16] In the future, salivary pepsin concentration in reflux event monitoring and time of day should be examined in research involving patients with laryngomalacia concurrently getting MII-pH testing.[5]

Understanding the negative effects of chronic aspiration on children's health and quality of life requires an understanding of the relationship between LM and swallowing dysfunction (SwD).[17] Although this link has not been quantitatively and objectively confirmed in studies, it is possible that LM can cause SwD because of an anatomical impairment that could lead to disarray in the suck-swallow-breathe rhythm, especially in newborns. The Jaffal et al. study's data, however, does not substantially corroborate this theory.[10] Compared to patients with mild LM, those with intermediate LM had a higher risk of aspirating or penetrating on FEES.[3] Given the vast range of reported incidence resulting from selective testing and variations in baseline features, the prevalence of swallowing difficulties in LM and GERD is a serious concern. Abnormal swallowing has been linked to conditions such as Down syndrome, GERD, and preterm, and secondary airway lesions (SAL) that can coexist with LM. When assessing the prevalence of SwD, the following factors must be taken into consideration.[10]

According to reports, GERD and LM frequently coexist, with acid reflux being present in 59% of 1295 children who have laryngomalacia. In 28 children with SwD, instrumental testing has demonstrated an objective improvement in laryngeal sensory function and swallowing after GERD therapy.[10] SwD has been linked to prematurity; infants born before 34 weeks of pregnancy have a higher risk of aspiration or penetration on videofluoroscopic swallowing studies (VFSS).[18] Another possible confounding factor is Down syndrome, where some studies utilizing objective tests have reported an overall higher frequency of SwD (up to 72%).[19] Still, silent aspiration is a relevant issue because, if instrumental examination is limited to children exhibiting symptoms, a significant number of children may go undiagnosed or underdiagnosed.[10]

In their analysis of the treatment of laryngomalacia, Duncan et al. concentrated on the effects of thickening formula and acid suppression in the management of oropharyngeal dysphagia.[11] Results indicated that thickening feeds may be more advantageous than suppressing acid, as it did not lower the risk of hospitalization or supraglottoplasty. The majority of primary care pediatricians are the ones who administer acid-suppressing drugs to these patients. The severity of laryngomalacia has a major influence on the results, with moderate-to-severe cases more likely to need surgical therapy. Even after accounting for the severity of the condition and any coexisting conditions, receiving acid suppression therapy for mild laryngomalacia raises the chance of supraglottoplasty.[11] According to recent research, suppressing acid may not lessen extraesophageal symptoms and might instead make matters worse.[20] Since over 70% of acid suppression prescriptions are written before a patient sees a subspecialist, educational outreach to specialists and primary care physicians is necessary to limit the use of acid suppression in newborns.[11]

Breast milk or formula thickening is a common treatment for laryngomalacia, a common kind of GER in infants. Thickening may help babies with laryngomalacia because it has been demonstrated to lessen reflux symptoms and the quantity of refluxate that reaches the oropharynx.[21] In this susceptible group, undiagnosed or inadequately managed oropharyngeal dysphagia may lead to worse outcomes. It needs a multidisciplinary team, including speech-language pathologists, to teach the family the proper thickening technique and nipple flow rates. The use of acid suppression is associated with a higher chance of hospitalization, a quicker time to supraglottoplasty, and an increased risk of supraglottoplasty even after adjusting for concomitant illnesses and the severity of the disease. Additionally, it doesn't seem to improve the laryngomalacia results. Oropharyngeal dysphagia is nevertheless common in infants with laryngomalacia, and it may be a treatable condition that is overlooked in this patient group.[11]

## CONCLUSION

Recent research on laryngomalacia (LM) has focused on the outcomes of surgical treatments, but there is a lack of evidence regarding its natural progression and spontaneous resolution. Studies have revealed a link between LM and pepsin, a reliable diagnostic marker, but no significant differences have been found. Pepsin is a common comorbidity in LM patients and serves as a biomarker for airway reflux, but research has revealed its harmful impact on proximal airways. Further investigation is necessary to comprehend pepsin's role in LM pathophysiology and its connection to swallowing dysfunction. Although acid suppression treatment for laryngomalacia is prevalent, it does not reduce the risk of supraglottoplasty or hospitalizations.

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