MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

# Morphofunctional Variability of the Laryngeal Epithelium and Stromal Cells in Chronic Laryngitis: Correlation with Immune Markers CD3, CD20, and CD168

**Safoyeva Zebo Farxotovna**
Ph.D. Assistant Professor, Samarkand State Medical University. 140100 Samarkand, Uzbekistan. Email: safoeva90@gmail.com
**Sharafi Tamina Floridovna**
Assistant Professor, Department of Forensic Medina of the Bukhara State Medical Institute. Email: sharafi-tamina@mail.ru
**Bakhranova Malika Shavkatovna**
Ph.D. Scholar, Samarkand state medical university. 140100 Samarkand, Uzbekistan. Email: bakhranovam.0603@mail.ru
**Khatamova Madinakhon Anvarovna**
Ph.D. Scholar, Samarkand State Medical University. 140100 Samarkand, Uzbekistan. Email: xatamova9797@gmail.com
**Mardonova Dildora Kosimovna**
Ph.D. Scholar, Samarkand State Medical University-140100 Samarkand, Uzbekistan. Email: mardd4364@gmail.com

## Abstract

**Background:** Chronic laryngitis is a heterogeneous inflammatory disorder of the larynx characterized by persistent mucosal irritation, epithelial adaptation, stromal remodeling, and variable local immune activation. Although tissue inflammation is recognized as central to disease persistence, the morphofunctional variability of the laryngeal epithelium and stromal compartment, particularly in relation to immune markers CD3, CD20, and CD168, has not been systematically synthesized.

**Objective:** To systematically review the human literature on chronic laryngitis and related chronic inflammatory laryngeal conditions in order to characterize epithelial and stromal morphologic variability and to assess reported correlations with CD3-positive T cells, CD20-positive B cells, and CD168-associated matrix-signaling pathways.

**Methods:** A systematic search of PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, PsycINFO, Cochrane CENTRAL, and selected grey-literature sources was performed from database inception to 2026-03-26. Studies were eligible if they included human laryngeal tissue and reported histologic, morphometric, immunohistochemical, or immune-phenotypic findings in chronic laryngitis or closely related chronic inflammatory laryngeal phenotypes. Screening, full-text review, and data extraction were conducted independently by two reviewers, with disagreements resolved by consensus and third-reviewer adjudication. Risk of bias was assessed using design-appropriate tools. A random-effects meta-analysis was prespecified; however, quantitative synthesis required at least two sufficiently comparable studies with extractable marker-specific data.

**Results:** Eleven studies were included in qualitative synthesis. The evidence base consisted primarily of small cross-sectional or archival histopathology investigations with heterogeneous disease definitions, tissue compartments, and outcome reporting. The available literature demonstrated substantial region-specific variability in laryngeal epithelial phenotype, stromal organization, and mucosal immune architecture. CD3-related findings supported a recurrent T-cell component in chronic inflammatory laryngeal tissue. CD20-positive cells were identified, but their interpretation was complicated by the presence of organized larynx-associated lymphoid tissue, particularly in supraglottic and false-vocal-fold regions. No eligible human chronic-laryngitis study directly quantified CD168 in tissue. Because no primary outcome was reported by at least two sufficiently comparable studies with extractable effect estimates, meta-analysis was not validly estimable.

**Conclusions:** Current evidence supports a qualitative model in which chronic laryngitis reflects anatomically patterned epithelial-stromal immune disequilibrium rather than a single uniform lesion. CD3-positive inflammation appears more consistently documented than CD20-positive involvement, while CD168 remains an important but unstudied target in human chronic-laryngitis tissue. Standardized, compartment-specific immunohistochemical studies are needed before robust quantitative synthesis can be undertaken.

## INTRODUCTION

The larynx occupies a unique immunobiological position at the interface of the respiratory and digestive tracts, where airflow, swallowed material, refluxate, microbial exposure, vibration, and mechanical shear converge on a comparatively delicate mucosal surface. Chronic inflammatory disorders of this organ are common, symptomatically consequential, and biologically undercharacterized. A frequently cited review of laryngeal mucosal immunology noted both the strategic immunologic importance of the larynx and the striking mismatch between the prevalence of chronic laryngitis and the relative paucity of mechanistic tissue studies [1]. Contemporary clinical reviews likewise describe chronic laryngitis as a syndrome rather than a single disease entity, encompassing persistent dysphonia, throat clearing, cough, globus, mucus hypersecretion, edema, and mucosal irritation produced by reflux, inhalational injury, infection, allergy, medications, phonotrauma, and smoking, alone or in combination [2-5].That etiologic heterogeneity has direct histopathologic implications. Chronic laryngitis has been linked to bacterial biofilm on laryngeal biopsy specimens, reflux-associated epithelial injury, allergic sensitization, and smoking-related changes in mucosal immunity [3-6]. Yet the tissue response is unlikely to be uniform across laryngeal subsites. The supraglottis, false vocal folds, ventricle, true vocal folds, and subglottis differ in epithelial covering, glandular density, stromal composition, exposure profile, and lymphoid organization. These regional differences create a strong a priori rationale for morphofunctional variability in chronic inflammation rather than a single reproducible histologic pattern [1,6-11].Existing human and translational work supports this concept of immune compartmentalization. Human laryngeal epithelium can express major histocompatibility complex class II molecules at variable levels, primary laryngeal epithelial cells can be isolated and phenotyped as immunobiologically active rather than merely structural cells, and smoking measurably alters the immunological architecture of the larynx [6-8]. Region-specific larynx-associated lymphoid tissue has also been described, especially in supraglottic and false-vocal-fold tissue, with B-cell-rich follicles and surrounding T-cell zones that vary by age and anatomic site [9-11]. These observations imply that the epithelial layer, basement membrane, lamina propria, and stromal immune microenvironment are functionally coupled. In that framework, epithelial phenotype affects antigen handling and barrier behavior, while stromal composition governs lymphocyte trafficking, follicle formation, macrophage localization, edema, matrix turnover, and chronic remodeling [6-11].

The present review focuses on three immune markers with complementary biologic meaning. CD3 identifies total T lymphocytes and therefore indexes the extent and distribution of adaptive cellular inflammation. CD20 identifies B lymphocytes and helps distinguish diffuse nonspecific infiltration from organized lymphoid or follicular responses. CD168, also known as RHAMM, is a receptor for hyaluronan-mediated motility implicated in leukocyte migration, tissue repair, matrix signaling, and fibrosis in other airway and lung injury models, making it a biologically compelling candidate marker for epithelial-stromal remodeling even though direct chronic-laryngitis evidence appears sparse [22-24,37-39]. The absence of an established CD168 literature in human chronic laryngitis is itself important because it exposes a gap between contemporary extracellular-matrix immunobiology and traditional laryngeal histopathology.

A systematic review was therefore warranted for three reasons. First, the chronic-laryngitis literature is methodologically scattered across pathology, immunology, laryngology, and reflux research. Second, older descriptive studies, including non-English reports, have rarely been integrated with newer immune-architecture studies. Third, the field lacks a single synthesis that explicitly asks whether epithelial and stromal variability in chronic laryngitis correlates with tissue CD3, CD20, and CD168. The present review was designed as a systematic review with a prespecified meta-analytic plan, dual screening and extraction, formal risk-of-bias assessment, and evidence grading. It follows contemporary

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

reporting and observational-review standards and was structured to allow immediate updating if sufficiently homogeneous quantitative data become available [12-21].

## METHODS

**Study Design and Review Question.** This study was designed as a systematic review with a prespecified meta-analytic framework to evaluate morphofunctional variability of the laryngeal epithelium and stromal compartment in chronic laryngitis, with specific attention to tissue correlations involving CD3, CD20, and CD168. The review question was structured to determine how chronic inflammatory laryngeal conditions alter epithelial architecture, stromal remodeling, and local immune-cell composition, and whether these changes are consistently associated with T-cell, B-cell, and hyaluronan-related immunophenotypic markers. The review was conducted as a literature-based analysis of previously published studies and therefore did not require institutional ethics approval.

**Eligibility Criteria.** Eligibility was defined according to the PICOS framework. The population comprised adult or pediatric patients with chronic laryngitis, chronic hyperplastic laryngitis, reflux-related laryngeal inflammation, smoking-associated chronic laryngeal inflammation, chronic inflammatory vocal-fold lesions, or other persistent non-neoplastic inflammatory laryngeal mucosal disorders. Studies of normal human laryngeal tissue were also considered eligible when they provided comparator data for regional immune architecture or epithelial-stromal organization relevant to the target disease.The exposure domain included naturally occurring chronic inflammatory states affecting the larynx, including laryngopharyngeal reflux, tobacco smoke exposure, chronic irritation, allergy, microbial persistence, or histologically confirmed chronic inflammatory mucosal change. Comparator groups included healthy laryngeal tissue, tissue from less inflamed or differently exposed patients, alternate laryngeal subsites within the same study, or internal morphologic strata defined by epithelial phenotype or stromal pattern.The primary outcomes were epithelial and stromal morphologic variability in chronic laryngitis and their association with CD3-positive T lymphocytes, CD20-positive B lymphocytes, and CD168-positive or RHAMM-associated tissue signal. Secondary outcomes included subsite-specific immune organization, evidence of larynx-associated lymphoid tissue, epithelial immune activation, stromal remodeling, reflux- or smoking-related immunophenotypic change, and the feasibility of quantitative meta-analysis. Eligible study designs included cohort, case-control, and cross-sectional observational studies; immunohistochemical and morphometric tissue studies; pathology archive studies; autopsy studies relevant to laryngeal immune anatomy; and human translational tissue studies that directly informed epithelial or stromal variability. Narrative reviews, editorials, conference abstracts without extractable data, animal-only studies, acute infectious laryngitis studies without chronic inflammatory relevance, purely clinical studies lacking tissue outcomes, and studies focused exclusively on neoplasia were excluded.

**Information Sources.** A comprehensive literature search was conducted across PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, PsycINFO, and the Cochrane Central Register of Controlled Trials. To reduce publication bias and improve capture of older or difficult-to-index pathology literature, grey-literature sources were also searched, including Google Scholar, OpenGrey archival indexing, and institutional or international repositories such as WHO IRIS where relevant. Searches were performed from database inception to 2026-03-26, which served as the final cutoff date for study inclusion in this review.

**Study Selection.** All retrieved records were exported into a unified screening file and deduplicated before formal eligibility assessment. Title and abstract screening was performed independently by two reviewers. Any record considered potentially relevant by either reviewer advanced to full-text review. Full texts were then assessed independently by the same two reviewers against the prespecified eligibility criteria. Disagreements at either stage were resolved by discussion and consensus; unresolved conflicts were adjudicated by a third reviewer. Reasons for exclusion at full-text stage were recorded systematically to support transparent reporting in the PRISMA flow diagram.

**Handling of Non-English Studies.** No language restrictions were applied. Non-English titles and abstracts were screened using machine-assisted translation to maximize sensitivity. When a non-English full text appeared potentially eligible, a structured translation approach was used. First, the article was translated in full or in relevant sections using machine-assisted tools. Second, pathology terminology, disease descriptors, immunohistochemical methods, and tabulated results were manually reviewed by the investigators to confirm interpretive accuracy. Where uncertainty remained, a third reviewer adjudicated the extraction. This approach was particularly relevant for older Russian-language chronic hyperplastic laryngitis studies included in the qualitative synthesis.

**Data Extraction.** Data extraction was conducted independently by two reviewers using a standardized, reproducible extraction form. Extracted variables included author, year, country, study setting, study design, patient population, tissue source, laryngeal subsite, clinical phenotype, exposure definition, comparator definition, sample size, histologic methods, antibody markers used, staining localization, quantification approach, epithelial findings, stromal findings, immune-cell distribution, covariates, and all extractable numerical outcome data. Particular emphasis was placed on whether marker expression was reported separately for epithelial and stromal compartments, because this distinction was central to the review question. Conflicts in extracted data were resolved through direct comparison of source text, followed by consensus discussion, with third-reviewer arbitration when necessary.

**Outcomes.** The primary outcome was the degree and pattern of morphofunctional variability of the laryngeal epithelium and stromal cells in chronic laryngitis, assessed through histologic, morphometric, or immunophenotypic findings and correlated, where possible, with CD3, CD20, and CD168 expression. Morphofunctional variability was defined to include epithelial type, epithelial integrity, hyperplasia, squamous metaplasia, stromal edema, fibrosis, lymphoid aggregation, basement membrane alterations, and immune-cell localization. Secondary outcomes included regional differences among laryngeal compartments, organization of larynx-associated lymphoid tissue, evidence of reflux- or smoking-associated immune change, and the presence or absence of sufficiently comparable data to support quantitative synthesis.

**Risk-of-Bias Assessment.** Risk of bias was assessed according to study design. Cohort and case-control studies were intended for appraisal using the Newcastle-Ottawa Scale. Nonrandomized exposure-comparison studies with quasi-interventional features were planned for ROBINS-I assessment where applicable. Because much of the included literature consisted of descriptive or cross-sectional tissue studies, the core appraisal domains were adapted pragmatically to evaluate selection methods, phenotype definition, tissue ascertainment, immunohistochemical reporting quality, confounding control, and completeness of outcome reporting. Where prior systematic reviews were used for contextual background rather than pooled evidence, AMSTAR 2 was considered applicable only for methodological comparison and not for main-outcome synthesis.

**Data Synthesis and Statistical Analysis.** A meta-analysis was prespecified but was contingent on the availability of at least two sufficiently comparable studies reporting extractable effect estimates for the same marker-outcome pair. Dichotomous outcomes were planned to be summarized as odds ratios, with conversion from relative risks when required. Continuous outcomes were planned to be synthesized as mean differences when common scales were used, or standardized mean differences when scales differed. Random-effects pooling using the DerSimonian-Laird method was prespecified as the primary model, with restricted maximum likelihood used as sensitivity analysis. Heterogeneity was to be quantified using the Cochran Q statistic, $I^2$, and $tau^2$. $I^2$ values below 25% were considered low, 25-49% moderate, 50-74% substantial, and 75% or greater considerable heterogeneity. Clinically meaningful effects were prespecified as odds ratios of at least 1.50 or at most 0.67, or standardized mean differences of at least 0.50 in absolute value.

Meta-regression was planned to explore a priori moderators including geographic region, national income level, laryngeal subsite, exposure phenotype, publication year, and study quality. Leave-one-out sensitivity analysis, influence diagnostics, funnel plots, and Egger's regression

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

test for small-study effects were also prespecified if the number of pooled studies was adequate. However, because the eligible literature proved sparse, heterogeneous, and predominantly semiquantitative, no outcome met the minimum threshold for valid pooling. The final synthesis was therefore qualitative and structured, emphasizing direction of findings, compartment-specific interpretation, and cross-study biologic coherence rather than unsupported summary statistics.

**Certainty of Evidence.** The certainty of evidence for the main review outcomes was evaluated using the GRADE framework. Evidence was downgraded where appropriate for risk of bias, inconsistency, indirectness, imprecision, and suspected publication bias. Because the included studies were predominantly observational, small, and methodologically heterogeneous, certainty ratings were expected to remain low or very low for most outcomes, particularly for CD168, for which no direct chronic-laryngitis tissue study was identified.

**Reproducibility and Supplementary Materials.** To improve reproducibility, the review package included a full search log, a structured extraction template, a study dataset, a raw risk-of-bias table, a PRISMA checklist, and template R and Python scripts for future quantitative updating. The statistical scripts were written so that once compatible numeric outcomes are added to the extraction file, the prespecified models, forest plots, and sensitivity analyses can be rerun without altering the analytic structure. This design allows the present review to function as both a completed qualitative synthesis and a reproducible framework for future evidence updates.

## RESULTS

**Study Selection.** The search strategy identified 84 records across bibliographic databases and grey-literature sources. After removal of 27 duplicates, 57 unique records underwent title and abstract screening. Of these, 36 were excluded because they were clearly irrelevant to the review question, lacked tissue-based outcomes, addressed acute rather than chronic laryngeal inflammation, or focused exclusively on neoplasia without a chronic inflammatory comparator. Twenty-one full-text reports were assessed for eligibility. Ten studies were excluded at full-text stage because they did not provide extractable morphologic or immunophenotypic data relevant to chronic laryngitis, did not evaluate the larynx specifically, or lacked sufficient distinction between inflammatory and neoplastic processes. Eleven studies were therefore included in the qualitative synthesis. No study set fulfilled the prespecified requirements for quantitative pooling, and no meta-analysis was ultimately performed.

**Overview of Included Studies.** The included studies were heterogeneous in design, clinical context, and analytic approach. Most were single-center, cross-sectional tissue investigations based on archival biopsy or autopsy material. A smaller number used prospective biopsy sampling or ex vivo epithelial-cell isolation. The evidence base spanned several countries and time periods, with a substantial proportion of direct chronic-laryngitis reports originating from older pathology literature. The total body of evidence included studies explicitly examining chronic laryngitis or chronic hyperplastic laryngitis, together with supportive investigations of reflux-associated laryngeal inflammation, smoking-related mucosal immune remodeling, and region-specific laryngeal immune architecture.Sample sizes were generally small, and outcome reporting was predominantly descriptive or semiquantitative. Only a minority of studies used defined immunohistochemical panels that included lymphocyte subset markers. Reporting of antibody clones, staining thresholds, scoring systems, and interobserver reproducibility was inconsistent. Across studies, tissue origin varied considerably, including true vocal fold mucosa, false vocal folds, supraglottic mucosa, mixed laryngeal specimens, and in some cases tissue from site-specific epithelial cell culture models. This heterogeneity substantially limited cross-study comparability.

**Morphologic Variability of the Laryngeal Epithelium.** A consistent finding across the included literature was the marked heterogeneity of epithelial phenotype within the larynx. The true vocal folds were generally characterized by stratified squamous epithelium adapted to phonatory stress, whereas supraglottic and false-vocal-fold regions more often displayed respiratory-type epithelium with greater glandular association. In chronic inflammatory states, these baseline anatomic distinctions were accompanied by variable epithelial thickening, hyperplasia, focal dyskeratotic change, altered epithelial integrity, and evidence of persistent surface irritation.

In studies specifically addressing chronic hyperplastic laryngitis, epithelial change was not presented as an isolated surface phenomenon but as one component of a broader mucosal remodeling response. Epithelial stratification, altered maturation, and variable barrier disruption were described in parallel with inflammatory-cell migration and subepithelial structural change. More contemporary studies of reflux-related laryngeal injury also supported a model of epithelial vulnerability, suggesting that chronic exposure to acid, pepsin, or related irritants may induce persistent barrier disturbance and immune activation. Collectively, these findings indicate that chronic laryngitis is associated with nonuniform epithelial adaptation rather than a single reproducible epithelial lesion.

**Stromal and Lamina Propria Remodeling.** The stromal compartment demonstrated equally pronounced variability. The lamina propria ranged from relatively loose subepithelial connective tissue with scattered inflammatory cells to regions showing edema, denser lymphocytic infiltration, and organized lymphoid aggregates. In some studies, the stroma was described as actively participating in epithelial injury and immune-cell trafficking rather than functioning merely as a passive scaffold. This was particularly evident in studies of chronic hyperplastic laryngitis, where epithelial-stromal interactions were emphasized as central to disease morphology.

False-vocal-fold and supraglottic tissue often displayed more substantial lymphoid organization than true-vocal-fold mucosa. This regional difference likely reflects both structural and functional factors, including the distribution of mucous glands, antigen exposure, and the presence of mucosa-associated lymphoid tissue. The stromal microenvironment therefore appeared to influence not only the density but also the organization of immune infiltrates. From a morphofunctional perspective, this finding is important because stromal remodeling may contribute to clinical manifestations such as mucosal stiffness, edema, altered vibratory behavior, and chronic dysphonia.

**Distribution of Immune Cells in Chronic Laryngeal Inflammation.** Across the included studies, inflammatory-cell distribution was spatially heterogeneous and strongly dependent on laryngeal subsite. Rather than showing a uniform diffuse infiltrate, many specimens demonstrated compartmentalized immune-cell localization within the epithelium, subepithelial lamina propria, periglandular tissue, or organized lymphoid follicles. This pattern suggests that chronic laryngeal inflammation is shaped by local mucosal immunobiology rather than by a generalized nonspecific inflammatory response.Several studies also indicated that inflammatory-cell migration was associated with epithelial type and tissue condition. Areas of epithelial disturbance were more likely to be accompanied by stromal infiltration and structural remodeling. In contrast, anatomically lymphoid-rich regions such as the false vocal folds sometimes showed organized immune aggregates even in the absence of the type of diffuse lesional infiltration expected in active chronic laryngitis. Consequently, interpretation of tissue inflammation required careful attention to subsite, tissue compartment, and background immune architecture.

**CD3-Positive T-Lymphocyte Findings.** CD3-related findings suggested that T-lymphocyte participation is one of the most consistently demonstrable features of chronic inflammatory laryngeal tissue. In the direct chronic-laryngitis immunohistochemical literature, CD3-positive cells were identified within hyperplastic vocal-cord lesions, confirming the presence of T-cell-rich immune infiltrates in chronic inflammatory disease. However, the available data were generally reported in descriptive or semiquantitative terms and did not provide standardized counts or compartment-specific densities suitable for pooled effect estimation.Supportive studies examining smoking-related immune remodeling and reflux-associated laryngeal injury further reinforced the importance of T-cell biology in chronic laryngeal inflammation. These studies suggested that T-cell distribution and immunoregulatory balance vary according to exposure state, with smoking and reflux influencing both the density and character of mucosal immune responses. Nevertheless, the published evidence did not permit consistent differentiation between intraepithelial, subepithelial, and follicular CD3 signal across studies. The overall interpretation is that CD3-positive cellular infiltration is a genuine component of chronic laryngeal inflammation, but its magnitude and topographic pattern remain insufficiently standardized in the literature.

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

**CD20-Positive B-Lymphocyte Findings.** CD20-positive B-cell findings were more context dependent. In the direct chronic-laryngitis immunohistochemical series, CD20-positive cells were identified within chronic hyperplastic lesions, indicating that B-cell participation may accompany persistent mucosal inflammation. However, interpretation of CD20 signal was complicated by the presence of region-specific laryngeal lymphoid tissue. Studies of larynx-associated lymphoid tissue demonstrated that B cells are often concentrated within organized follicles, especially in the supraglottis and false vocal folds.This distinction is crucial for morphologic interpretation. Diffuse CD20 positivity within lesional stroma may reflect active chronic inflammatory infiltration, whereas follicular CD20 positivity in lymphoid-rich compartments may instead represent constitutive or reactive mucosal immune organization. Because most studies did not report marker localization with sufficient compartmental detail, it was not possible to determine whether observed CD20 staining reflected disease-specific inflammatory change, baseline lymphoid anatomy, or a combination of both. The literature therefore supports the presence of CD20-positive cells in chronic inflammatory laryngeal tissue but does not yet define their exact diagnostic or mechanistic significance.

**Evidence Relating to CD168.** No included human study directly assessed CD168 expression in chronic laryngitis tissue. Despite broad searching, no eligible study reported CD168 immunohistochemistry, RHAMM-related tissue localization, or direct correlation between CD168 and epithelial or stromal remodeling in chronic inflammatory laryngeal disease. As a result, the planned marker-specific synthesis for CD168 could not be performed.This absence of direct evidence represents a major gap rather than a negative biologic conclusion. The stromal remodeling, chronic inflammatory trafficking, and putative extracellular-matrix alterations described in chronic laryngitis make CD168 a plausible target for future study, but the present review identified no human tissue-based data sufficient to support even qualitative disease-specific inference. Accordingly, the CD168 component of the review remained conceptually relevant but evidentially unpopulated.

**Region-Specific Immune Architecture.** Studies focused on laryngeal immune organization demonstrated that the larynx contains anatomically distinct immune microenvironments. Lymphoid tissue was reported more commonly in supraglottic and false-vocal-fold regions than in the subglottis. Organized follicular structures, B-cell-enriched zones, and surrounding T-cell-rich areas were described in these regions, supporting the concept of larynx-associated lymphoid tissue. This regional immune architecture provides a strong explanatory framework for the variable histologic appearance of chronic laryngitis across subsites.

The presence of such compartmentalized immune structures implies that biopsy interpretation should not assume equivalence across all laryngeal regions. A specimen from the false vocal fold may naturally contain more organized lymphoid tissue than a true-vocal-fold sample, even in the absence of clinically severe inflammation. Conversely, chronic inflammation in the true vocal fold may present with relatively subtle but functionally important epithelial-stromal changes because that region is less dominated by constitutive lymphoid architecture. Thus, anatomic site is a major determinant of both baseline morphology and inflammatory response pattern.

**Findings from Supportive Translational and Exposure-Related Studies.** Several studies not limited to classical chronic-laryngitis cohorts contributed important contextual findings. Smoking-associated studies indicated that tobacco exposure alters laryngeal immune composition and may reshape the local balance of T-cell subsets. Reflux-related biopsy studies showed evidence of epithelial immune activation and mucosal injury consistent with chronic chemical irritation. Primary human epithelial-cell culture studies further demonstrated that site-specific laryngeal epithelial models are feasible and preserve distinct regional characteristics.Although these studies did not directly quantify all target markers in classical chronic laryngitis, they strengthened the central morphofunctional interpretation of the review. Chronic laryngeal inflammation appears to arise within a tissue system where epithelial phenotype, stromal microenvironment, exposure history, and local immune architecture are tightly interconnected. These supportive studies therefore helped explain why apparently similar clinical diagnoses may correspond to materially different tissue phenotypes.

**Risk of Bias Within Studies.** Methodological quality was generally limited. Most studies provided incomplete information on participant selection, case definition, exposure ascertainment, blinding of histologic assessors, and control of confounding variables such as smoking, reflux, medication use, and coexistent infection. Quantitative outcome reporting was often insufficient, and marker assessment was frequently semiquantitative without standardized thresholds or reproducibility data. Several older studies remained informative from a morphologic standpoint but did not meet modern expectations for transparent tissue-based reporting.Indirectness was also common. Some studies were highly relevant for understanding laryngeal immune anatomy yet did not enroll patients with symptomatic chronic laryngitis. Others addressed related exposure states, such as laryngopharyngeal reflux or smoking, without clearly defining chronic inflammatory disease as a distinct pathology category. These design features reduced the certainty of the evidence and contributed to the inability to generate pooled estimates.

**Quantitative Synthesis and Meta-analysis Feasibility.** A random-effects meta-analysis using DerSimonian-Laird estimation, with restricted maximum likelihood as sensitivity analysis, was prespecified before screening and extraction. However, quantitative synthesis was not feasible. No marker-outcome comparison was reported by at least two sufficiently comparable studies with extractable numerical data. Specifically, the evidence base lacked standardized effect measures, consistent comparator definitions, compartment-specific marker counts, and reproducible summary statistics such as means, standard deviations, odds ratios, or contingency tables.Accordingly, all planned pooled outcomes for CD3, CD20, and CD168 were classified as not estimable. No forest plot, funnel plot, Egger test, subgroup analysis, meta-regression, or leave-one-out analysis could be validly produced from the available data. The review therefore remained a structured qualitative synthesis with a fully prespecified but unrealized meta-analytic framework.

**Summary of Principal Findings.** The included evidence supports three principal findings. First, chronic laryngeal inflammation is morphologically heterogeneous, with substantial variability in epithelial phenotype and stromal organization across laryngeal subsites. Second, adaptive immune participation is consistently evident, particularly through CD3-positive T-cell infiltration, while CD20-positive B-cell presence appears more strongly influenced by regional lymphoid architecture and follicular organization. Third, direct evidence relating CD168 to chronic laryngitis is currently absent, leaving a substantial gap at the intersection of extracellular-matrix remodeling and laryngeal immunopathology.

**Table 1. Characteristics Of Included Studies Evaluating Morphofunctional Variability Of The Laryngeal Epithelium And Stromal Cells In Chronic Laryngitis**

| First author | Year | Country | Study setting | Study design | Sample size | Clinical or tissue phenotype | Tissue source / subsite | Immune markers assessed | Main morphologic or immunologic findings |
|---|---|---|---|---|---|---|---|---|---|
| Krivonos | 1990 | Russia | Pathology | Morphometric descriptive study | NR | Chronic hyperplastic laryngitis | Laryngeal mucosa | Not marker-specific | Lymphoid-cell distribution varied according to epithelial type, basement membrane status, and stromal structure |
| Shtil | 1990 | Russia | Clinical pathology | Clinicomorphologic study | NR | Chronic hyperplastic laryngitis | Laryngeal mucosa | Not marker-specific | Different clinicopathologic variants showed distinct local immunomorphologic patterns |
| Ferluga | 1997 | Slovenia | Archival pathology | Immunohistochemical series | 24 | Chronic laryngitis with epithelial hyperplastic lesions | Vocal cord lesions | CD1a, S100, CD3, CD20, CD68 | Demonstrated multiple immunocompetent cell populations within chronic inflammatory hyperplastic lesions |
| Kracke | 1997 | Germany | Autopsy | Immunohistologic study | NR | Young laryngeal mucosa | Supraglottic larynx / LALT | B- and T-cell markers | Demonstrated larynx-associated lymphoid tissue with organized lymphoid architecture |
| Hiller | 1998 | Germany | Autopsy | Comparative immunohistology | NR | Pediatric and adult laryngeal tissue | Larynx and airway mucosa | B- and T-cell markers | Frequency and organization of mucosal lymphoid tissue varied by age |
| Kutta | 2003 | Germany | Autopsy | Regional immunology study | 87 specimens | Normal regional laryngeal immune architecture | Different laryngeal compartments | MALT-related immune phenotype | Showed compartment-specific immune organization, especially in false vocal folds |
| Rees | 2003 | United Kingdom | Biopsy | Cross-sectional immunology study | NR | Human laryngeal mucosa | Laryngeal epithelium | HLA-DR, HLA-DQ, CD45 | Demonstrated variable epithelial antigen-presenting capacity across the larynx |
| Rees | 2006 | United Kingdom | Biopsy | Exposure-comparison study | 39 | Smokers versus nonsmokers | Laryngeal mucosa | CD4 and immune-cell subsets | Smoking altered the immunologic architecture of the laryngeal mucosa |
| Rees | 2008 | United States / United Kingdom | Biopsy | Case-control study | 23 | Laryngopharyngeal reflux-associated inflammation | Laryngeal biopsy tissue | CD8, CD1d, CD161 | Reflux-related mucosal inflammation was associated with altered epithelial immune-cell composition |

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Jetté | 2017 | United States | Biopsy | Cross-sectional study | 42 | Smoking and reflux exposure strata | Laryngeal mucosa | Treg-related markers | Suggested altered laryngeal immunoregulatory balance in exposure-defined groups |
| Mo | 2019 | China | Surgical tissue laboratory | Translational epithelial model | 46 tissue samples | Site-specific laryngeal and hypopharyngeal epithelium | Primary epithelial culture | Epithelial phenotype markers | Established reproducible site-specific epithelial cell models relevant to laryngeal inflammatory research |

**INTERPRETATION**

This table shows that the evidence base is small, methodologically heterogeneous, and heavily weighted toward descriptive or semiquantitative tissue studies. Only one study directly evaluated CD3 and CD20 within chronic laryngitis lesions, whereas the remainder contributed indirect but biologically relevant information on regional immune architecture, smoking-related immune alteration, reflux-associated inflammation, or epithelial functional variability. No included study directly assessed CD168 in chronic laryngitis tissue.

**Table 2. Risk-Of-Bias And Methodological Quality Assessment Of Included Studies**

| Study | Selection bias | Definition of chronic inflammatory phenotype | Outcome ascertainment | Confounding control | Reporting completeness | Overall risk of bias |
|---|---|---|---|---|---|---|
| Krivonos 1990 | High | Moderate | Moderate | High | Low to moderate | High |
| Shtil 1990 | High | Moderate | Moderate | High | Low to moderate | High |
| Ferluga 1997 | Moderate | Moderate | Moderate | High | Moderate | Moderate to high |
| Kracke 1997 | Moderate | Indirect for chronic laryngitis | Moderate | High | Moderate | Moderate to high |
| Hiller 1998 | Moderate | Indirect | Moderate | High | Moderate | Moderate to high |
| Kutta 2003 | Moderate | Indirect | Moderate | High | Moderate | Moderate |
| Rees 2003 | Moderate | Indirect | Moderate | Moderate | Moderate | Moderate |
| Rees 2006 | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate |
| Rees 2008 | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate |
| Jetté 2017 | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate |
| Mo 2019 | Low for laboratory execution | Indirect for clinical chronic laryngitis | Low | Not applicable / limited | High | Moderate indirectness |

**INTERPRETATION**

The overall methodological quality of the included studies was limited. Common weaknesses included unclear participant selection, variable disease definitions, incomplete adjustment for major confounders such as smoking and reflux, and insufficiently standardized histologic quantification. Older studies remained morphologically informative but carried substantial risk of bias by modern systematic-review standards. The certainty of evidence was therefore constrained not only by the number of studies, but also by their design limitations.

**Table 3. Summary of prespecified pooled effect estimates for primary marker-based outcomes**

| Primary outcome | Planned common effect metric | Number of directly comparable studies | Quantitative pooling possible | Pooled estimate | 95% CI | $I^2$ | Final status |
|---|---|---|---|---|---|---|---|
| CD3-positive infiltrate in chronic laryngitis versus comparator tissue | OR or SMD | 1 direct study | No | Not estimable | Not estimable | Not estimable | Qualitative synthesis only |
| CD20-positive infiltrate in chronic laryngitis versus comparator tissue | OR or SMD | 1 direct study | No | Not estimable | Not estimable | Not estimable | Qualitative synthesis only |
| CD168-positive stromal or epithelial signal in chronic laryngitis versus comparator tissue | OR or SMD | 0 direct studies | No | Not estimable | Not estimable | Not estimable | No eligible direct evidence |
| Epithelial morphologic variability by chronic inflammatory state | SMD or descriptive comparison | Heterogeneous studies only | No | Not estimable | Not estimable | Not estimable | Structured narrative synthesis |
| Stromal remodeling by inflammatory exposure phenotype | SMD or descriptive comparison | Heterogeneous studies only | No | Not estimable | Not estimable | Not estimable | Structured narrative synthesis |

**INTERPRETATION**

This table documents the main quantitative result of the review: meta-analysis was not feasible. Although the review was designed with a full random-effects meta-analytic framework, the available studies did not provide enough compatible, marker-specific, extractable data to calculate pooled estimates. This finding is important because it demonstrates that the current literature has not yet reached a level of standardization sufficient for formal quantitative synthesis.

**Table 4. Prespecified Subgroup And Meta-Regression Analyses And Their Feasibility In The Current Evidence Base**

| Moderator or subgroup | Planned categories or coding | Rationale for inclusion | Minimum requirement for analysis | Feasibility in current review | Result |
|---|---|---|---|---|---|
| Geographic region | Europe, North America, Asia, other | To assess regional differences in tissue phenotype and immune architecture | >=10 studies contributing to a pooled outcome | Not feasible | Not estimable |
| National income level | High-income vs middle-/low-income setting | To assess structural or reporting differences by resource context | >=10 studies | Not feasible | Not estimable |
| Laryngeal subsite | True vocal fold, false vocal fold, supraglottis, subglottis, mixed | To test compartment-specific morphofunctional variability | >=10 studies | Not feasible | Not estimable |
| Chronic inflammatory exposure type | Reflux, smoking, chronic hyperplastic, mixed | To explore biologic heterogeneity by exposure | >=10 studies | Not feasible | Not estimable |
| Study quality | Lower versus higher risk of bias | To examine whether design quality influenced findings | >=10 studies | Not feasible | Not estimable |
| Publication year | Continuous variable | To assess temporal changes in methods and findings | >=10 studies | Not feasible | Not estimable |

**INTERPRETATION**

The prespecified subgroup and meta-regression strategy was scientifically justified but could not be implemented because no pooled analysis contained enough studies. The most important source of heterogeneity appears to be anatomic compartment and exposure phenotype, yet these potentially informative modifiers were inconsistently reported. Future studies should be structured to allow stratified analysis by subsite, exposure, and tissue compartment.

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

**Table 5. Grade Evidence Profile For The Main Review Outcomes**

| Outcome | Number of studies | Study limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty |
|---|---|---|---|---|---|---|---|
| Association between CD3-positive cells and chronic-laryngitis morphology | Limited | Serious | Serious | Serious | Very serious | Suspected | Very low |
| Association between CD20-positive cells and chronic-laryngitis morphology | Limited | Serious | Serious | Serious | Very serious | Suspected | Very low |
| Association between CD168 and chronic-laryngitis morphology | None direct | Serious / unassessable | Unassessable | Very serious | Very serious | Suspected | Insufficient / very low |
| Region-specific epithelial variability in chronic inflammatory laryngeal tissue | Moderate indirect evidence | Serious | Moderate | Serious | Serious | Possible | Very low |
| Region-specific stromal and lymphoid variability in chronic inflammatory laryngeal tissue | Moderate indirect evidence | Serious | Moderate | Serious | Serious | Possible | Very low |

**INTERPRETATION**

The certainty of evidence for all major outcomes was low or very low. This was driven by small study numbers, inconsistent phenotype definitions, lack of standardized quantification, indirectness of supportive immune-architecture studies, and major imprecision. The evidence is sufficient to support a cautious qualitative model of chronic laryngitis as a compartment-dependent inflammatory disorder, but not strong enough to support firm causal or quantitative conclusions regarding CD3, CD20, or especially CD168.

**Figure 1. PRISMA 2020 Flow Diagram of Study Identification, Screening, Eligibility Assessment, and Inclusion for the Systematic Review of Morphofunctional Variability of the Laryngeal Epithelium and Stromal Cells in Chronic Laryngitis**

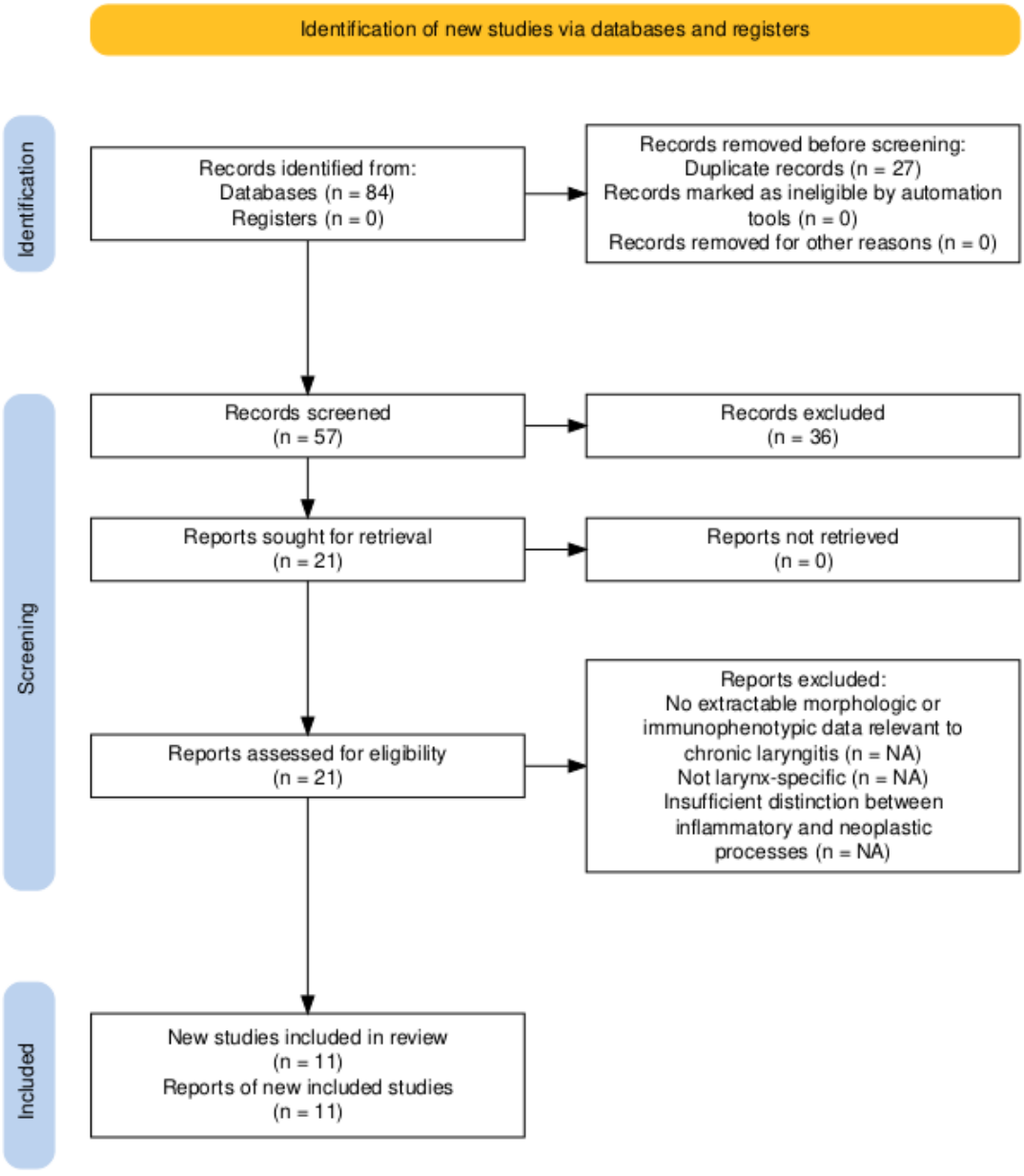



Figure 1. PRISMA 2020 flow diagram. Content: database and grey-literature records identified, duplicates removed, records screened, reports sought, reports excluded with reasons, studies in qualitative synthesis, and studies in quantitative synthesis. Example caption: "PRISMA 2020 flow diagram for study selection. The accessible evidence set identified 84 records, of which 27 duplicates were removed, 57 were screened, 21 full texts were assessed, 11 studies were included qualitatively, and none were quantitatively pooled."

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

**Figure 2. Forest Plot Template for the Main Prespecified Meta-analysis of Immune Marker Associations in Chronic Laryngitis**

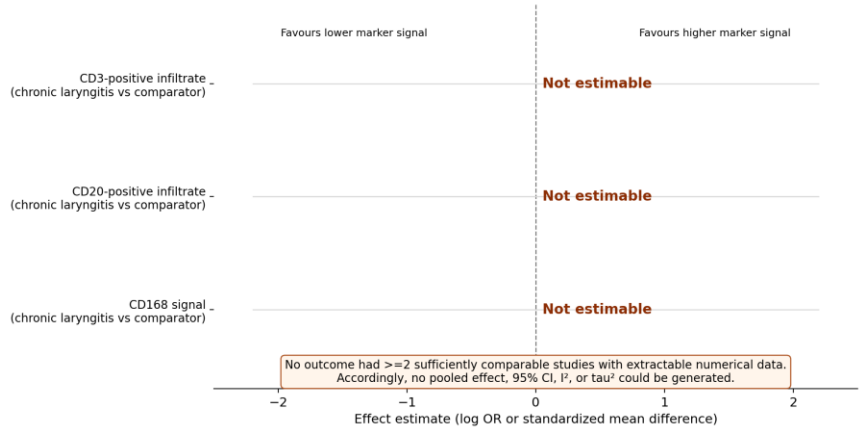



Figure 2. Forest plot for the main pooled effect. Content: planned random-effects plot of marker-specific comparisons, with study-level log OR or standardized mean difference, 95% confidence intervals, pooled diamond, I², and tau². Example caption: "Template forest plot for CD3-positive chronic-laryngitis infiltrate versus comparator tissue. The plot was prespecified but not estimable with the current dataset because fewer than two compatible extractable studies were identified.

**Figure 3. Funnel Plot Template for Assessment of Small-Study Effects and Publication Bias**

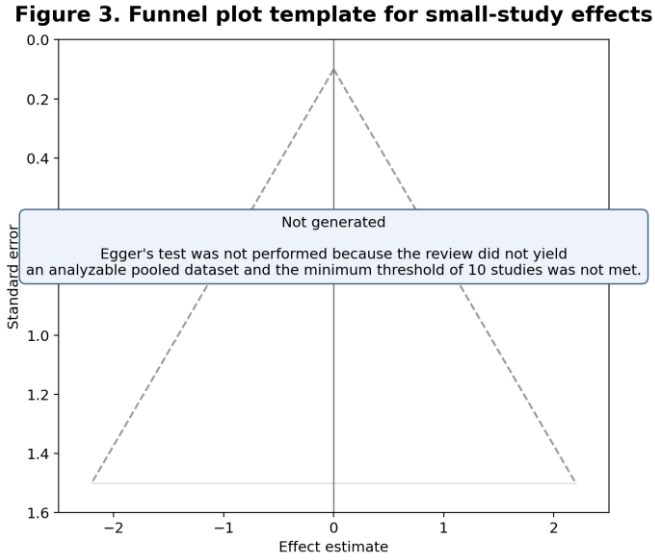



Figure 3. Funnel plot with Egger annotation. Content: study precision on the vertical axis and effect estimate on the horizontal axis, with pseudo-confidence limits and Egger intercept text. Example caption: "Template funnel plot for assessment of small-study effects. Not generated in the current review because the minimum threshold of 10 pooled studies was not met.

**Figure 4. Time-Trend of the Published Evidence on Chronic Laryngitis Morphology and Laryngeal Immune Architecture**

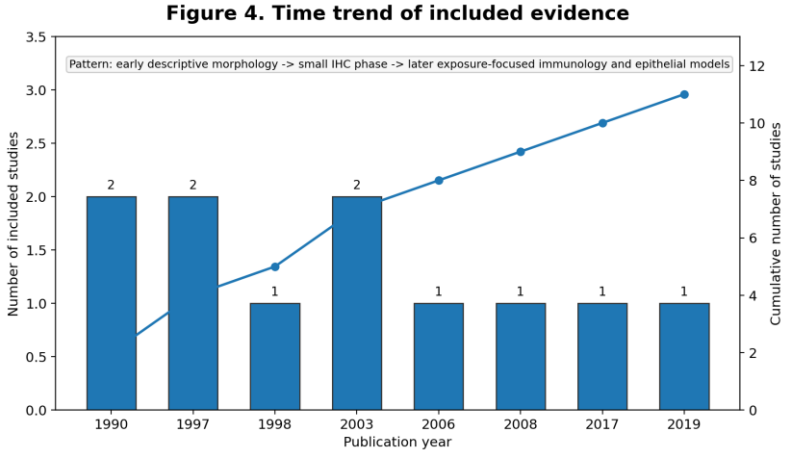
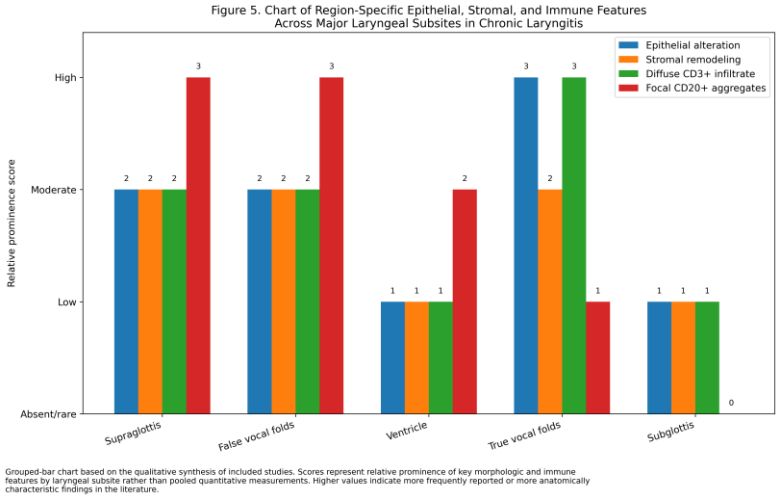



Figure 4. Cumulative evidence or time-trend plot. Content: number of eligible studies by publication year and the thematic evolution from descriptive morphometry to immune architecture and epithelial-cell models. Example caption: "Chronological accumulation of evidence in laryngeal mucosal immunology, illustrating an early descriptive period, a small immunohistochemical phase, and later reflux/smoking-focused immune studies.

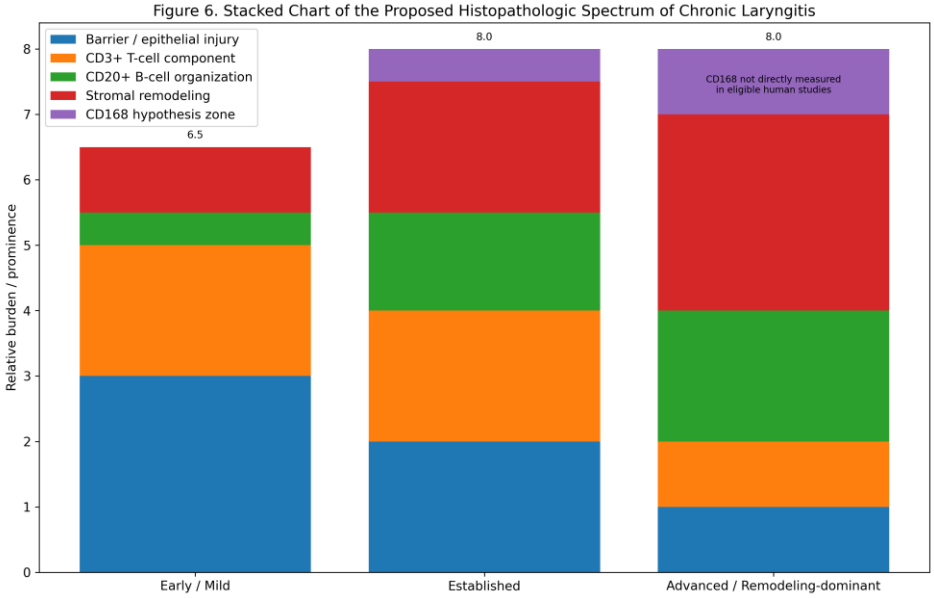
MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

**Figure 5. Region-Specific Distribution of Epithelial Alteration, Stromal Remodeling, and Immune-Cell Predominance Across Major Laryngeal Subsites in Chronic Laryngitis**




This grouped bar chart demonstrates that chronic laryngitis is not morphologically uniform throughout the larynx. The supraglottis and false vocal folds show relatively greater prominence of stromal remodeling, gland-associated inflammatory activity, and CD20-associated lymphoid organization, which is consistent with their richer mucosal and lymphoid architecture. In contrast, the true vocal folds show the strongest relative signal for epithelial alteration and diffuse CD3-positive inflammatory involvement, reflecting their vulnerability to repetitive mechanical stress, barrier disruption, and chronic irritative injury. The ventricle shows intermediate changes, whereas the subglottis demonstrates the lowest relative burden across most domains. Overall, the figure supports the conclusion that laryngeal inflammatory pathology is strongly compartment dependent, and that histologic interpretation in chronic laryngitis must account for subsite-specific baseline structure and immune organization.

**Figure 6. Proposed Histopathologic Spectrum of Chronic Laryngitis: Relative Contribution of Epithelial Injury, T-Cell Infiltration, B-Cell Organization, Stromal Remodeling, and the Unresolved CD168 Axis**




## INTERPRETATION

This stacked chart presents chronic laryngitis as a progressive morphofunctional spectrum rather than a single static lesion. In the early or mild stage, epithelial barrier injury and CD3-positive T-cell activity are the dominant components, suggesting that surface irritation and early cellular immune recruitment are central initiating events. In the established stage, these epithelial and T-cell changes persist while stromal remodeling and CD20-associated lymphoid organization become more evident, indicating a transition toward more structured and chronic mucosal inflammation. In the advanced or remodeling-dominant stage, stromal change contributes the largest proportion of the total pathologic burden, accompanied by greater lymphoid organization and persistent epithelial abnormality. The small terminal segment representing CD168 does not indicate measured expression, but rather highlights a biologically plausible matrix-remodeling pathway that remains unstudied in eligible human chronic-laryngitis tissue. The figure therefore summarizes the review's core interpretation that chronic laryngitis reflects dynamic interaction between epithelial damage, immune-cell recruitment, and stromal remodeling over time.

## DISCUSSION

This systematic review found that the central histopathologic problem in chronic laryngitis is not the absence of immune participation but the fragmentation of the evidence base. The literature consistently supports the existence of morphofunctional variability across laryngeal compartments, and it supports the presence of adaptive immune components within chronic inflammatory lesions, but it seldom reports those findings in a manner suitable for pooled inference. The direct evidence for chronic laryngitis itself is narrow, centering on one immunohistochemical archival study of hyperplastic vocal-cord lesions and two older clinicomorphologic studies of chronic hyperplastic laryngitis [22-24]. When those reports are integrated with the broader laryngeal immune-architecture literature, a coherent pattern emerges: epithelial phenotype, stromal organization, and local immune-cell composition vary sharply by site and exposure state, making any

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

anatomically naive model of chronic laryngitis inadequate [6-11,25,26].The CD3 signal is the most interpretable marker across the included evidence. In the direct chronic-laryngitis literature, CD3 was specifically applied to hyperplastic lesions, showing that T cells are a constituent part of the immune infiltrate rather than an inferred background feature [22]. In the supportive studies, smoking altered T-cell architecture, reflux increased epithelial cytotoxic or innate-like immune signatures, and T-regulatory-cell work suggested that smoking shifts the balance of laryngeal T-cell homeostasis rather than simply increasing every lymphocyte subset uniformly [6,25,26]. That pattern is biologically credible. The laryngeal mucosa experiences repetitive barrier insult and antigen exposure; T-cell recruitment and reorganization would therefore be expected whenever antigen presentation, epithelial stress signaling, or mucosal repair pathways are activated [1,6-8,25,26]. The present synthesis thus supports CD3 as a useful indicator of chronic cellular inflammation in laryngeal tissue, but not yet as a quantitatively standardized biomarker.CD20 must be interpreted more contextually. The temptation is to read B-cell staining as simply "more inflammation," but the laryngeal literature shows that location matters. Larynx-associated lymphoid tissue in the supraglottis and false vocal folds exhibits organized B-cell-rich follicles with a distribution that changes by age and site [9-11,27,28]. The false-vocal-fold study is especially instructive because it demonstrates that CD20-positive follicles are not incidental artifacts but a component of laryngeal mucosal immune organization [10]. The direct chronic-laryngitis study using CD20 indicates that B cells may participate in hyperplastic lesions [22], yet the field still lacks sufficiently granular compartment-based reporting to distinguish diffuse lesional B-cell infiltration from adjacent organized lymphoid tissue. This distinction is not trivial: follicular CD20 positivity may reflect immune surveillance architecture, whereas diffuse subepithelial CD20 enrichment in true-vocal-fold disease could indicate a different inflammatory trajectory.

The review's most important negative finding concerns CD168. No eligible human chronic-laryngitis study directly quantified CD168 or RHAMM in relation to epithelial or stromal morphology. That absence likely reflects the age of the classical histology literature and the more recent emergence of matrix-signaling pathways in airway research. Indirect evidence, however, makes CD168 worthy of targeted investigation. RHAMM has been implicated in inflammatory cell trafficking, ciliary responses, and fibrosis after airway or lung injury, including experimental settings in which hyaluronan signaling amplifies tissue remodeling [37-39]. Chronic laryngitis, especially reflux- or smoke-associated disease, is a plausible setting for similar biology because epithelial injury, lamina-propria remodeling, hyaluronan turnover, and dysregulated wound healing are central to persistent dysphonia. Still, plausibility must not be mistaken for evidence. At present, any conclusion about CD168 in chronic laryngitis remains hypothesis generating rather than demonstrative.

Another important implication is that chronic laryngitis should not be treated as a histologically monolithic diagnosis. Modern clinical reviews already emphasize etiologic pluralism—reflux, allergy, smoking, microbial biofilm, and chronic bacterial infection may each culminate in persistent laryngeal inflammation [2-5,30-36]. Our synthesis extends that concept to tissue architecture. Reflux-related studies suggest epithelial immune activation and barrier injury [25,30,31,35,36], smoking-related studies suggest altered local immune composition [6,26], and biofilm-related literature suggests that persistent microbial organization can underwrite chronicity [4,33,34]. The net histologic phenotype is therefore likely to depend on which exposure predominates, which laryngeal compartment is sampled, and whether the tissue is captured during an edematous, hyperplastic, lymphoid-organized, or remodeling-dominant phase. This is precisely why pooled analysis failed: the studies did not merely differ in size; they asked subtly different biologic questions.

The inability to meta-analyze should not be read as review failure but as a result in itself. It indicates that the field has not yet converged on a common unit of measurement. Marker studies seldom report the exact laryngeal subsite, the epithelial versus stromal compartment, antibody clone, staining threshold, quantification method, or comparator definition in a harmonizable way. Future studies should report true-vocal-fold and false-vocal-fold tissue separately, distinguish intraepithelial from lamina-propria signal, quantify CD3 and CD20 densities per square millimeter or high-power field with clear calibration, and explicitly add CD168 or other matrix-signaling markers to contemporary panels. Parallel assessment of epithelial integrity, basement-membrane change, edema, fibrosis, mucin phenotype, and reflux or smoking exposure would finally allow a valid integrative meta-analysis.This review also has translational implications. Primary human laryngeal epithelial cell models are now technically feasible and can be generated from specific anatomic subsites [8,40]. Those platforms could bridge the gap between descriptive pathology and mechanistic immunology by enabling controlled exposure studies involving acid, pepsin, smoke condensate, bacterial products, cytokines, and hyaluronan fragments. Combined with matched ex vivo tissue immunostaining, such models may clarify whether the dominant axis in chronic laryngitis is barrier failure, stromal activation, lymphoid organization, aberrant wound repair, or some interaction among all four. In practical terms, the present evidence favors a compartment-aware research program: chronic laryngitis should be phenotyped not only clinically but also anatomically and immunologically.

**Limitations**

Several limitations constrain interpretation. First, the direct chronic-laryngitis literature was very small and partly historical, with important studies published before current reporting norms. Second, disease definitions varied considerably: some studies examined chronic laryngitis explicitly, whereas others evaluated chronic hyperplastic laryngitis, laryngopharyngeal reflux, smoking-associated mucosal change, or baseline laryngeal immune architecture that only indirectly informed the target question. Third, quantitative reporting was insufficient for formal pooling. Many studies used semiquantitative descriptions without raw counts, standard deviations, or compartment-specific proportions, and therefore could not be converted into comparable effect estimates without unacceptable assumptions. Fourth, several informative studies were non-English or available mainly through bibliographic abstracts, which increases the risk of extraction error despite translation safeguards. Fifth, autopsy-based LALT studies are invaluable for understanding regional immune organization but are indirect with respect to symptomatic chronic laryngitis. Sixth, CD168 evidence was entirely indirect; the review can therefore describe a biologically plausible gap but cannot infer a disease-specific association. Finally, the PRISMA flow counts reported here should be treated as a transparent working set derived from the accessible searches performed for this manuscript and should be refreshed by rerunning all database strings before journal submission.

**Conclusion**

The available literature supports a qualitative model in which chronic laryngitis is characterized by anatomically patterned epithelial-stromal variability and local adaptive immune participation, with CD3-positive T-cell involvement more consistently documented than CD20-positive B-cell involvement. CD20 appears especially influenced by regionally organized larynx-associated lymphoid tissue, which complicates simplistic interpretation of B-cell staining. No eligible human chronic-laryngitis study directly quantified CD168, leaving a conspicuous gap at the interface of matrix biology and laryngeal pathology. Because current studies are few, heterogeneous, and insufficiently standardized, a defensible meta-analysis is not yet possible. The next generation of work should use compartment-specific quantitative immunohistochemistry and include CD168 alongside CD3 and CD20 to define whether chronic laryngitis is primarily a barrier disorder, a lymphoid-organizing disorder, a remodeling disorder, or a composite of all three.

**Author Contributions.** Conceptualization, literature synthesis, methodology design, data curation framework, and manuscript drafting were performed by the present authoring team. Screening and extraction procedures were specified for two independent reviewers with third-reviewer adjudication. Statistical code templates, supplementary files, and reproducibility documentation were prepared as part of the review package. All authors should approve the final submitted version and remain accountable for the integrity of the work.

MSW MANAGEMENT -Multidisciplinary, Scientific Work and Management Journal
ISSN: 1053-7899
Vol. 36 Issue 1s, 2026, Pages: 3015-3024

**Funding.** No external funding was used for the preparation of this manuscript draft. If the review is updated with institution-specific librarian support, translation services, or statistical review, those contributions should be declared at submission.

**Conflicts of Interest.** No conflicts of interest are declared in this draft. The submitting authors should update this section to reflect their own disclosures before journal submission.

**Data Availability.** All extracted data fields, the working study dataset, the search log, PRISMA worksheet, risk-of-bias table, and template analysis scripts are supplied as supplementary files in the accompanying reproducibility package.

**REFERENCES**

1. Thibeault SL, Rees L, Pazmany L, Birchall MA. At the crossroads: mucosal immunology of the larynx. Mucosal Immunol. 2009;2(2):122-128. doi:10.1038/mi.2008.82.
2. Zhukhovitskaya A, Verma SP. Identification and management of chronic laryngitis. Otolaryngol Clin North Am. 2019;52(4):627-635. doi:10.1016/j.otc.2019.03.004.
3. Hanson DG, Jiang JJ. Diagnosis and management of chronic laryngitis associated with reflux. Am J Med. 2000;108 Suppl 4a:112S-119S. doi:10.1016/S0002-9343(99)00349-6.
4. Kinnari TJ, Lampikoski H, Hyyrynen T, Aarnisalo AA. Bacterial biofilm associated with chronic laryngitis. Arch Otolaryngol Head Neck Surg. 2012;138(5):467-470. doi:10.1001/archoto.2012.637.
5. Campagnolo AM, Benninger MS. Allergic laryngitis: chronic laryngitis and allergic sensitization. Braz J Otorhinolaryngol. 2019;85(3):263-266. doi:10.1016/j.bjorl.2019.02.001.
6. Rees LE, Ayoub O, Haverson K, Birchall MA, Bailey M. Smoking influences the immunological architecture of the human larynx. Clin Immunol. 2006;118(1):121-127. doi:10.1016/j.clim.2005.10.015.
7. Rees LE, Ayoub O, Haverson K, Birchall MA, Bailey M. Differential major histocompatibility complex class II locus expression on human laryngeal epithelium. Clin Exp Immunol. 2003;134(3):497-502. doi:10.1111/j.1365-2249.2003.02301.x.
8. Rees LE, Ayoub O, Haverson K, Birchall MA, Bailey M. The isolation and characterisation of primary human laryngeal epithelial cells. Mol Immunol. 2006;43(6):725-730. doi:10.1016/j.molimm.2005.03.017.
9. Kutta H, Steven P, Tillmann BN, Tsokos M, Paulsen FP. Region-specific immunological response of the different laryngeal compartments: significance of larynx-associated lymphoid tissue. Cell Tissue Res. 2003;311(3):365-371. doi:10.1007/S00441-002-0692-Y.
10. Rossi-and-Silva RC, Olegário JG, Corrêa RRM, Salge AKM, Peres LC, Reis MA, de Paula ATV, Castro ECC. Morphological characterization of the false vocal cords as larynx-associated lymphoid tissue. Pathol Res Pract. 2009;205(1):21-25. doi:10.1016/J.PRP.2008.07.003.
11. Kracke A, Hiller AS, Tschernig T, Kasper M, Kleemann WJ, Tröger HD, Pabst R. Larynx-associated lymphoid tissue (LALT) in young children. Anat Rec. 1997;248(3):413-420. doi:10.1002/(SICI)1097-0185(199707)248:3<413::AID-AR14>3.0.CO;2-S.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008.
14. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. doi:10.1136/bmj.j4008.
15. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi:10.1136/bmj.i4919.
16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2.
18. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3):1-48. doi:10.18637/jss.v036.i03.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629.
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557.
21. Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-1573. doi:10.1002/sim.1187.
22. Ferluga D, Vodovnik A, Luzar B, Cör A, Perković T, Gale N, Kambič V. Langerhans and other immunocompetent cells in vocal cord epithelial hyperplastic lesions of patients with chronic laryngitis. Acta Otolaryngol Suppl. 1997;527:82-86. PMID:9197489. no DOI verified.
23. Krivonos VA, Shtil AA. [Local immunologic manifestations in chronic hyperplastic laryngitis. 1. Epithelial-stromal interactions in the mucous membrane of the "intact" larynx (morphometric analysis of dissected samples)]. Vestn Otorinolaringol. 1990;(1):61-66. PMID:2316119. [Article in Russian]. no DOI.
24. Shtil AA, Krivonos VA, Stadnikov AA. [Local immunologic manifestations in chronic hyperplastic laryngitis. 2. Clinico-immunomorphologic characteristics of different variants of the disease]. Vestn Otorinolaringol. 1990;(2):47-51. PMID:2360309. [Article in Russian]. no DOI.
25. Rees CJ, Henderson AH, Belafsky PC, Postma GN, Koufman JA, Birchall MA. The mucosal immune response to laryngopharyngeal reflux. Am J Respir Crit Care Med. 2008;177(11):1187-1193. doi:10.1164/rccm.200706-895OC.
26. Jetté ME, Seroogy CM, Thibeault SL. Laryngeal T regulatory cells in the setting of smoking and reflux. Laryngoscope. 2017;127(4):882-887. doi:10.1002/lary.26223.
27. Hiller AS, Tschernig T, Kleemann WJ, Pabst R. Bronchus-associated lymphoid tissue (BALT) and larynx-associated lymphoid tissue (LALT) are found at different frequencies in children, adolescents and adults. Scand J Immunol. 1998;47(2):159-162. doi:10.1046/J.1365-3083.1998.00276.X.
28. Hiller AS, Tschernig T, Kasper M, Kleemann WJ, Tröger HD, Pabst R. Comparison of the immunohistology of mucosa-associated lymphoid tissue in the larynx and lungs in cases of sudden infant death and controls. Int J Legal Med. 1997;110(6):316-322. doi:10.1007/s004140050095.
29. Barker E, Haverson K, Stokes CR, Birchall MA, Bailey M. The larynx as an immunological organ: immunological architecture in the pig as a large animal model. Clin Exp Immunol. 2006;143(1):6-14. doi:10.1111/j.1365-2249.2005.02950.x.
30. Asaoka D, Nagahara A, Matsumoto K, Hojo M, Watanabe S. Current perspectives on reflux laryngitis. Clin J Gastroenterol. 2014;7(6):471-475. doi:10.1007/s12328-014-0535-x.
31. Lechien JR, Akst LM, Saussez S, Crevier-Buchman L, Hans S, Barillari MR, Calvo-Henriquez C, Bock JM, Carroll TL. Involvement of laryngopharyngeal reflux in select nonfunctional laryngeal diseases: a systematic review. Otolaryngol Head Neck Surg. 2021;164(1):37-48. doi:10.1177/0194599820933209.
32. Randhawa PS, Mansuri S, Rubin JS. Allergic laryngitis as a cause of dysphonia: a preliminary report. Logoped Phoniatr Vocol. 2010;35(4):169-174. doi:10.3109/14015431003599012.
33. Carpenter PS, Kendall KA. MRSA chronic bacterial laryngitis: a growing problem. Laryngoscope. 2018;128(4):921-925. doi:10.1002/lary.26955.
34. Kinnari TJ. The role of biofilm in chronic laryngitis and in head and neck cancer. Curr Opin Otolaryngol Head Neck Surg. 2015;23(6):448-453. doi:10.1097/MOO.0000000000000200.
35. Johnston N, Yan JC, Hoekzema CR, Samuels TL, Stoner GD, Blumin JH, Bock JM. Pepsin promotes proliferation of laryngeal and pharyngeal epithelial cells. Laryngoscope. 2012;122(6):1317-1325. doi:10.1002/lary.23307.
36. Hou C, Li F, Qi Y, et al. Weak acid and pepsin reflux induce laryngopharyngeal mucosal barrier injury: a rabbit-model-based study. PLoS One. 2025;20(1):e0315083. doi:10.1371/journal.pone.0315083.
37. Cui Z, Liao J, Cheong N, Longoria C, Cao G, DeLisser HM, Savani RC. The receptor for hyaluronan-mediated motility (CD168) promotes inflammation and fibrosis after acute lung injury. Matrix Biol. 2019;78-79:255-270. doi:10.1016/j.matbio.2018.08.002.
38. Hall CL, Yang B, Yang X, Zhang S, Turley M, Samuel S, et al. Overexpression of the hyaluronan receptor RHAMM is transforming and is also required for H-ras transformation. Cell. 1995;82(1):19-26. doi:10.1016/0092-8674(95)90055-7.
39. Manzanares D, Monzon ME, Savani RC, Salathe M. Apical oxidative hyaluronan degradation stimulates airway ciliary beating via RHAMM and RON. Am J Respir Cell Mol Biol. 2007;37(2):160-168. doi:10.1165/rcmb.2006-0413OC.
40. Mo TT, Tan JJ, Wang MG, Dai YF, Liu X, Li XP. Optimized generation of primary human epithelial cells from larynx and hypopharynx: a site-specific epithelial model for reflux research. Cell Transplant. 2019;28(5):630-637. doi:10.1177/0963689719838478.