Association between laryngopharyngeal reflux, gastroesophageal reflux and recalcitrant chronic rhinosinusitis: A systematic review

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Association between Laryngopharyngeal Reflux, Gastroesophageal Reflux and Recalcitrant Chronic Rhinosinusitis: A Systematic Review.

Abstract

Objective: To investigate the association between laryngopharyngeal reflux (LPR), gastroesophageal reflux disease (GERD) and recalcitrant chronic rhinosinusitis (CRS).

Data sources: PubMed, Cochrane Library, and Scopus.

Review methods: Three investigators search database for studies investigating the relationship between LPR, GERD and recalcitrant CRS with or without polyposis. The following outcomes were investigated with PRISMA criteria: age; gender; reflux and CRS diagnosis; association outcomes and potential treatment outcomes. Authors performed a bias analysis of papers and provided recommendations for future studies.

Results: A total of 17 studies investigated the association between reflux and recalcitrant CRS. According to pharyngeal pH monitoring, 54% of patients with recalcitrant CRS reported hypo or nasopharyngeal acid reflux events. The numbers of hypo- and nasopharyngeal acid reflux events were significantly higher in patients compared to healthy individuals in 4 and 2 studies, respectively. Only one report did not find group differences. The proportion of GERD was significantly higher in CRS patients compared to controls, with a prevalence ranging from 32% to 91% of cases. No author considered nonacid reflux events. There was an important heterogeneity in the inclusion criteria; definition of reflux and association outcomes, limiting the draw of clear conclusion. Pepsin was found in sinonasal secretions more frequently in CRS patients than controls.

Conclusion: Laryngopharyngeal reflux and GERD may be a contributing factors of CRS therapeutic resistance, but future studies are still needed to confirm the association considering nonacid reflux event.

Key words: Laryngeal; Larynx; Otolaryngology; Head Neck Surgery; Voice; Rhinosinusitis; Sinusitis; Rhinitis.

Introduction

Chronic rhinosinusitis (CRS) is a significant health problem, considered as one of the most common chronic disorders in U.S. and Europe.[1,2] The pathophysiology of CRS is multifactorial but predominantly involves mucosal inflammation and barrier dysfunction, leading to edema, ostial obstruction, mucus stasis and changes in the sinus microbiome.[2] CRS is associated with ongoing symptoms, poor quality of life and unpredictable therapeutic responses.[1,3] Predisposing factors may include viral infection, asthma and allergy, immune deficiency, environmental etiologies (such as smoking or pollution) or combinations of several risk factors.[4-6] Over the last decades, laryngopharyngeal reflux (LPR) and gastroesophageal reflux disease (GERD) have been proposed as important contributing factors to a myriad of inflammatory upper aerodigestive tract diseases, including benign lesions of the vocal folds, otitis media, and chronic rhinosinusitis.[7-9] The prevalence of CRS has been shown to be higher in patients with LPR compare with controls,[10] and at the same time, CRS subjects have been shown to have higher rates of reflux disease when compared to those without CRS.[9] It has been proposed that CRS patients with reflux may be more recalcitrant to medical and surgical interventions.[6,8,11]

In this systematic review, we aimed to investigate the relationship between LPR, GERD and CRS recalcitrant to medical or surgical treatment.

Methods

The criteria for consideration of study inclusion were based on the population, intervention, comparison, outcome, timing and setting (PICOTS) framework.[12] For each study, two investigators (JRL, SS) independently reviewed and extracted data regarding the PRISMA checklist for systematic reviews.[13]

Patient population: Prospective or retrospective, controlled, uncontrolled, or randomized clinical studies published between 1980 and 2022 were considered. The studies had to be published in English, Spanish, or French peer-reviewed journals. Only clinical studies reporting data for more than 10 individuals were considered. Authors had to include adult patients with recalcitrant CRS with (CRSwNP) or without (CRSsNP) nasal polyposis[1] for whom the occurrence of reflux was investigated. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS),[1] recalcitrant CRS definition consisted of persistent symptoms despite appropriate treatment. According to the lack of international diagnosis consensus, the LPR diagnosis was based on symptoms, findings or objective examinations, e.g. gastrointestinal endoscopy, pH study or (hypopharyngeal-esophageal) multichannel intraluminal pH-impedance study ((HE)MII-pH). Patients with a LPR diagnosis based on symptoms and findings were considered as suspected LPR, whereas individuals with a pH monitoring diagnosis were considered as LPR patients. GERD was defined according DeMeester score, Montreal or Lyon guidelines.[7] There were no exclusion criteria based on age, ethnicity, socioeconomic status, and comorbidities. Importantly, note that the present systematic review focused on recalcitrant CRS and authors particularly investigated the methodology used for the LPR diagnosis, which are both differences with the previous review of Leason *et al*. who investigated the relationship between non-recalcitrant CRS and reflux.[9]

Intervention and comparison: Studies evaluating impact of reflux on the effectiveness of medical or surgical interventions for CRS were considered as well as investigations studying the prevalence of reflux in resistant/non-resistant CRS patients.

Outcomes: Two investigators (JRL, SS) reviewed the following outcomes: number of patients; age; gender ratio; CRS and reflux diagnoses; outcome association; potential treatment; and therapeutic outcomes. Moreover, investigators extracted other outcomes that

may contribute to CRS, e.g. allergy, occupational factors, tobacco, fungal disease, immunodeficiencies, ciliary disorders, cystic fibrosis, granulomatous diseases.

Timing and Setting: There was no criteria for specific stage or timing in the 'disease process' of the study population. Data from population-based registries or clinical hospital studies were considered.

Search strategy

The publication search was conducted on PubMED, Scopus, and Cochrane databases by three independent investigators (JRL, SS and AM). The databases were screened for abstracts and titles referring to the description of data of CRS and LPR patients. From the 3 investigators, 2 authors analyzed full texts of the selected publications. Findings of the search strategy were reviewed for relevance and the reference lists of these publications were examined for additional pertinent studies. Any discrepancies in synthesized data were discussed and resolved by the authors. The following keywords were included: 'larynx'; 'laryngeal'; 'reflux'; 'gastroesophageal'; 'laryngopharyngeal'; 'chronic'; 'refractory'; 'difficult-to-treat'; 'recalcitrant'; 'rhinosinusitis'; 'sinusitis'; 'sinus'. The type of study was classified according to the levels of evidence (I-V).[14] Authors also investigated findings from studies investigating effect of gastroduodenal reflux content into the nasal mucosa (e.g. pepsin, bile salts).

Bias analysis

The Tool to Assess Risk of Bias in Cohort Studies developed by the Clarity Group and Evidence Partners (McMaster University, Canada) was used by two authors (JRL & SS) for the bias/heterogeneity analyses of the included studies.[15] The bias analysis consisted of evaluation of cofactors that may impact the association/comparison of studies, i.e.

epidemiological (comorbidities, tobacco use, contributing factors, etc.); clinical; diagnosis approaches; and therapeutic characteristics of patient groups.

Results

A total of 512 articles were identified and 23 papers met our inclusion criteria (Figure 1). From them, 17 papers were dedicated to the association between recalcitrant CRSwNP or CRSsNP and reflux. Reflux was defined according to symptoms and signs, or pH study, or pepsin detection (Table 1).[4,8,16-30] There were 729 CRS patients (304 females), 187 suspected reflux patients, and 149 healthy individuals without reflux or CRS in the papers. Among studies, 47% of CRS patients were females (N=304/651). Gender ratio was not specified in one study.[29] The mean age of patients ranged from 39 to 61 yo. Six studies providing miscellaneous data about the association between reflux and sinonasal disorders that were not formally defined as CRS were excluded.[31-36]

Inclusion criteria and disorder definitions

Inclusion and exclusion criteria of studies are summarized in Table 2. The publication definitions of CRS are reported in Table 1. The definition of CRS was available for all studies, while no author clearly provided criteria to determine the CRS as recalcitrant to medical or surgical treatment. There were substantial differences between studies regarding the inclusion of patients with the following CRS factors: tobacco; allergy; and fungal infection. Smokers were included or excluded from the CRS patient samples in 5,[4,19,22,23,30] and 2 studies,[8,26] respectively. Three authors[4,22,23] included allergic CRS patients, while these patients were excluded in 6 studies.[8,16,24,27,28,30] DelGaudio and Wise *et al*. were the only authors who included fungal rhinosinusitis patients.[4,23] The most common exclusion criteria are described in Table 2 and included immune disorders,[8,22,24,27,28] immotile cilia

syndrome,[8,22,27,28] or cystic fibrosis.[8,16,22,26-28,35] Exclusion criteria were not reported in 6 studies.[4,17,18,20,21,23]

The inclusion criteria of control groups varied between studies (Table 2). Authors carefully investigated reflux,[17,18,21] or sinonasal symptoms[4,17,18,21,22,23,25,27,28] to select healthy individuals, while a few performed additional examinations, i.e. gastrointestinal (GI) endoscopy,[17,18,21] or CT-scan.[22,25,27,28] Tobacco consumption was an exclusion criteria for healthy individuals in one study.[21]

Sinonasal disorder definition

Seventeen investigations included patients with CRS.[4,8,16-30] The diagnosis criteria substantially varied across studies. The type of CRS was specified in 10 papers, consisting of CRSnNP [4,8,16,24,26-30] and/or CRSwNP.[4,21,24,26-30] Patients with refractory chronic rhinosinusitis to medical treatment were included in 7 studies,[16,20,22,25,27,28,30] while authors included individuals with recalcitrant CRS to medical and surgical treatment in 8 studies.[4,17-19,21,23,24,26] In 2 studies, patients had CRS without evidence of resistance to medical or surgical treatment.[8,29] The CRS diagnosis was based on symptoms, nasofibroscopy examination and CT-scan findings in 10 studies,[8,17-19,24-30] while authors did not perform CT-scan in 4 studies.[16,20,21,22] There was no information about the use of imaging for the CRS diagnosis in two studies.[4,23] Authors recognized to use European Position Paper on Rhinosinusitis (EPOS guidelines) for the CRS diagnosis in 4 papers.[8,16,27,28]

Reflux definition

The tools and criteria used for the reflux diagnosis are reported in Table 3. The following objective tools were used for the diagnosis: esophageal dual-probe pH monitoring;[19] hypopharyngeal-esophageal dual probe pH monitoring;[21,25] esophageal-hypopharyngeal

triple/quadruple-probe pH monitoring;[16-18,20] esophageal-hypo-nasopharyngeal triple-probe pH monitoring;[4,23] esophageal-nasopharyngeal triple-probe pH monitoring;[24] oropharyngeal single-probe pH monitoring;[26] multichannel intraluminal impedance pH monitoring; and pepsin detection.[22,27,28] A team based the reflux diagnosis on gastrointestinal endoscopy (esophagitis) and, therefore, considered GERD diagnosis.[8] LPR symptoms and signs were used to suspect reflux in two investigations.[29,30] The criteria used to determine the LPR diagnosis at the pH study substantially varied from one study to another (Table 3), as well as the conditions of the examination (antiacid meals or antireflux medication ON/OFF).

Association outcomes between chronic rhinosinusitis and reflux

Gastrointestinal and pH monitoring outcomes

The following outcomes were used to study the association between CRS and reflux: number of pharyngeal acid reflux events;[17,18,20,21,23,24] proximal esophageal acid exposure time;[19] reflux area index;[4,20,21] Ryan score;[26] distal esophageal reflux events/DeMeester score;[4,21] barium esophagogram findings;[18] esophageal motility;[18,19] GI endoscopy findings[4,8] and pepsin in nasal secretions or tissues.[22,25,27,28]

Among studies evaluating hypo/nasopharyngeal acid reflux events (pH<4), 54/99 (54%) CRS patients reported hypopharyngeal acid reflux events, ranging from 27% to 88% of included subjects.[17,18,20,25] Nasopharyngeal acid reflux events (pH<5) occurred in 39/115 (34%) CRS patients, ranging from 5% to 73% of cases [4,20,24] CRS patients reported significant higher number of hypopharyngeal (pH<4) or nasopharyngeal acid reflux events (pH<5) than healthy individuals in 4,[17,18,25,26] and 2 studies,[4,23] respectively. There were no significant differences in the number of nasopharyngeal acid reflux event in one study.[21] Three teams assessed pharyngeal reflux events in healthy individuals, and they reported that the hypopharyngeal and nasopharyngeal reflux events occurred in 11/31 (35%)[18,25] and 7/20 (35%)[4] of cases,

respectively. The proportion of GERD, defined regarding pH study or GI endoscopy findings, ranged from 32% to 91% of CRS cases.[4,8,20,21,24] Precisely, 100/155 (65%) CRS patients had GERD regarding international consensus guidelines. In 3 studies, the prevalence of GERD was significantly higher in CRS patients compared with controls.[4,21,24]

Pepsin detection outcomes

Pepsin was investigated in nasal secretions or tissues in 4 studies[22,25,27,28] with an overlap of patients in two studies.[27,28] Dinis *et al.* did not find significant differences in tissue pepsin concentrations between CRS and healthy individuals.[22] Ozmen *et al*. detected nasal lavage pepsin in 82% and 50% of LPR and healthy individuals, respectively; the group difference being significant.[25] Similar findings were found by Ren *et al*. and Wang *et al.* who reported significant higher concentrations of pepsin A in nasal secretions of CRS and CRSwNP patients compared with controls.[27,28]

Symptom and finding outcomes

Reflux or CRS symptoms and findings were studies in 6 papers. The following symptom severity tools were used: sinonasal outcome-20/22 (SNOT-20/22);[4,23,29,30] reflux finding score;[16,30] reflux symptom index (RSI);[16,23,29,30] or composed symptom score.[4,19] Brown *et al.* observed that patients with both CRS and suspected LPR reported higher scores of SNOT-22 and RSI than patients with only CRS or suspected LPR.[29] RSI, RFS and SNOT-22 significantly improved from pre- to post-FESS in patients with medically recalcitrant CRSnNP or CRSwNP.[30] RSI scores were significantly correlated with and SNOT-20 or SNOT-22 scores in CRS patients.[23,30]

Therapeutic outcomes

The impact of antireflux medication was investigated in 3 studies.[16,19,24] DiBiase *et al*. observed that CRS patients had modest nasal symptom improvements after 3-month proton pump inhibitors (PPIs) with/without antibiotics,[19] while Pincus *et al*. observed that 93% of patients with recalcitrant CRS reported significant symptom improvements after 4-week PPI therapy.[24] In a placebo-RCT, Anzic *et al*. observed better symptom and nasal finding improvements in 8-week PPI group compared with 8-week placebo group.[16]

Bias analysis

The systematic review included studies with the following level of evidence: IB (N=2), IIB (N=13), IIIb-IV (N=8). The bias analysis focused on CRS studies (Appendix 1). Overall, there was an important heterogeneity between studies about CRS and reflux diagnosis approaches. The CRS was adequately performed in 11/16 studies considering international diagnosis guidelines. The CRS diagnosis was not confirmed with imaging in 6 papers.[4,16,19,20,23,29] As reported in Table 2, the studies included various profiles of CRS, e.g. CRS with or without polyposis; fungal CRS or allergic CRS, which may be considered as an additional inclusion bias. Confounding factors of CRS or LPR clinical presentation were few considered in 8 studies,[4,16,19,23,24,25,29,30] while authors did not provide information in 4 studies.[17,18,20,21] There was no study considering both acid and nonacid hypo/nasopharyngeal reflux events for the LPR diagnosis or association analysis. The study of association between CRS and reflux was not performed with objective approach allowing the detection of reflux in pharyngeal region in 5 studies.[8,16,19,29,30]

Discussion

Chronic rhinosinusitis, gastroesophageal reflux and laryngopharyngeal reflux are prevalent diseases in Western countries and reflux has long time been suspected as an important

contributing factor of therapeutic resistance in CRS. However, the heterogeneity and the quality of studies exploring the role of GERD and LPR in CRS are low and do not allow clear conclusions to be drawn.

The primary limiting factor is the heterogeneity between research about the study populations. Depending on the studies, authors included patients with medical, both medical and surgical recalcitrant CRS with or without polyposis. Moreover, authors did not provide clear definition for recalcitrant CRS. Many additional clinical factors that may bias the study comparison (i.e. allergic, tobacco, fungal diseases) were excluded, included or ignored according to studies. The heterogeneity across studies regarding these outcomes may substantially impact the study results. Indeed, it has been demonstrated that the clinical features and therapeutic outcomes may be influenced by the characteristics of CRS (with or without polyposis), as well as by the occurrence of contributing factors, i.e. tobacco, allergy or asthma.[37-40] Similar findings were found for LPR.[7] For example, tobacco and allergy are known to be associated with laryngopharyngeal inflammation, LPR-like findings and symptoms.[7,41,42] In addition, tobacco may increase the number of reflux events through esophageal sphincter relaxation,[43] and, consequently, has to be considered in the study of the prevalence of reflux in recalcitrant CRS.

The overlap and non-specificity of CRS and LPR symptoms, and the impact of some comorbidities on the clinical pattern of diseases makes the use of objective diagnostic tools important. If the diagnostic approach of CRS seems reasonable in most studies, adhering to international consensus guidelines (EPOS), the diagnostic method of LPR is another important limiting factor. From a pathophysiological standpoint, it is known that LPR has significant pathophysiological differences with GERD.[7] GERD diagnosis is based on GI endoscopy findings (i.e. esophagitis) or occurrence of distal esophageal acid reflux events (pH<4) more than 6% of 24-jour testing time.[44] In practice, patients with hypopharyngeal

reflux events, and therefore LPR, did not commonly present GI endoscopy abnormalities or did not complete the pH study criteria for GERD diagnosis.[45-47] Interestingly, more than 50% of LPR disease are characterized by weakly and nonacid pharyngeal reflux events at the hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH).[46] Although there is no international consensus guidelines, most experts agree with the need to consider pH>4 reflux events to perform the diagnosis and to study potential associations.[47,48] The use of HEMII-pH is also imperative in the need to treat LPR in a more targeted fashion based on the acidity and location of the refluxate in the digestive tract; indirectly this affords more targeted therapies for recalcitrant CRS.[7] The importance to consider nonacid reflux events was supported by the findings of Delehaye *et al*. who suggested an important role of bile salts in the nasal mucociliary clearance.[31] The lack of consideration of hypo- and nasopharyngeal nonacid reflux events is therefore an important selection bias factors, excluding patients with nonacid LPR from some studies.

Future prospective studies are needed to investigate the role of reflux in recalcitrant CRS. Based on the findings of the present review, many factors should be considered, including the adherence to CRS diagnosis consensus guidelines; the definition and the features of recalcitrant CRS; the study of impact of predisposing CRS and LPR factors on association outcomes; the use of naso- or HEMII-pH for both diagnosis and study of association; and the use of more personalized disease treatments. The investigation of the role of the laryngopharyngeal/nasal microbiota on clinical and therapeutic features as well as the consideration of all gastroduodenal enzymes, and not only pepsin, are both additional growing important topics.

The main

Conclusion

The importance of reflux in the therapeutic resistance of CRS patients remains difficult to demonstrate regarding heterogeneity across studies in the diagnosis criteria, populations, and the lack of consideration of confounding factors and nonacid naso- or hypopharyngeal reflux events. Future clinical studies are needed and should consider all types of reflux and the detection of gastroduodenal enzymes in the tissue samples involved in the development and therapeutic resistance of CRS with or without polyps.

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There was an important heterogeneity in the inclusion criteria; definition of reflux and association outcomes, limiting the draw of clear conclusion. Pepsin was found in sinonasal secretions more frequently in CRS patients than controls.

Summary/Key points

-The prevalence of symptoms of LPR or GERD is high in patients with recalcitrant rhinosinusitis.

- According to pharyngeal pH monitoring, 54% of patients with recalcitrant CRS reported hypo or nasopharyngeal acid reflux events.

-The nonacid reflux events were not or poorly considered in studies.

-The importance of reflux in the therapeutic resistance of CRS patients remains difficult to demonstrate regarding heterogeneity across studies and the lack of use of objective testing for the LPR diagnostic such as HEMII-pH.

-Future clinical studies are needed and should consider all types of reflux and the detection of gastroduodenal enzymes in the tissue samples involved in the development and therapeutic resistance of CRS with or without polyps.

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Table 1: Features of studies investigating association between reflux and recalcitrant chronic rhinosinusitis.

References	Design	EL	Patients characteristics	CRS/LPR Diagnosis	Outcomes	Results (better values)	Findings
Ulualp (17) USA 1998	Prospective Controlled	IIB	Gr1=28 suspected LPR Gr2=12 CRS Gr3=6 CRS and suspected LPR Gr4=34 healthy subjects F/M (Gr1-4): 9/19-8/4-1/5-15/19 Age (Gr1-4): 49-48-54-40 yo	CRS: chronic symptoms despite medical and surgical treatments & positive fibroscopy & CT-scan. LPR: symptoms & signs.	Proportions of: Pharyngeal acid reflux event	Gr1 - Gr2 - Gr3 - Gr4 N=19-N=4-N=4-N=7 Gr1-3>Gr4	1. Patients with CRS reported higher proportion of pharyngeal acid reflux event than healthy controls.
Ulualp (18) USA 1999	Prospective Controlled	IIB	Gr1=11 resistant CRS Gr2=11 healthy individuals F/M (Gr1,2): 4/7 - 14/5 Age (Gr1,2): N.P.	CRS: chronic symptoms despite medical and surgical treatments & positive fibroscopy & CT-scan. LPR: pharyngeal acid event	Proportions of: Pharyngeal acid reflux event Barium esophagogram findings Reduced esophageal motility	Gr1-Gr2 N=7/11-0/11; Gr1>Gr2 GERD: N=5/11 N=2/11	1. Patients with CRS exhibited higher number of acid pharyngeal event than healthy individuals. All reflux events occurred upright.
DiBaise (19) Ireland 2002	Prospective Uncontrolled	IIB	Gr1= 11 CRS Gr2= 19 GERD F/M (Gr1,2): 4/7 - 14/5 Age (Gr1,2): 45 yo - 39 yo	CRS: 3-m symptoms despite medical and surgical treatments & positive fibroscopy or CT-scan. Median duration: 15 y LPR: esophageal acid event	Heartburn (1/w) Esophageal manometry Proximal acid exposure time Prevalence nasal symptoms	Gr1=8/11 Gr1=Gr2 Gr1=Gr2 Pre>Posttreatment	1. GERD was prevalent in patients with recalcitrant CRS. Many patients experienced modest nasal symptom improvement after 3-m omeprazole & antibiotics.
Wong (20) Australia 2004	Prospective Uncontrolled	IV	N=40 resistant CRS F/M: 25/15 Age: 56 yo	CRS: 3-m symptoms despite medical treatments & positive fibroscopy. No CT-scan LPR: nasopharyngeal acid event	Median Reflux Index GERD prevalence Hypopharyngeal acid event Nasopharyngeal acid event	4.2% N=12/37 N=10/37 N=2/37	1. 32.4% of CRS patients had abnormal 24-h pH studies but only 5% reported acid nasopharyngeal reflux events; 27% of patients had hypopharyngeal acid event.
Jecker (21) Germany 2005	Prospective Controlled	IIB	Gr1= 20 resistant CRSwp Gr2= 20 healthy controls F/M (Gr1,2): 9/11 - 10/10 Age (Gr1,2): 49 yo - 25 yo	CRS: 3-m symptoms despite medical and surgical treatments & positive fibroscopy & CT-scan. LPR: esophageal-hypopharyngeal acid event at the same time.	Distal esophageal acid event DeMeester score Reflux Area Index Hypopharyngeal acid event	Gr1>Gr2 N=11/20; Gr1>Gr2 Gr1>Gr2 Gr1=Gr2	1. recalcitrant CRS patients had higher GERD and acid esophageal reflux event than healthy controls. There was no difference between CRS and healthy subjects about pharyngeal acid event.

References	Design	EL	Patients characteristics	CRS/LPR Diagnosis	Outcomes	Results (better values)	Findings
DelGaudio (4) USA 2005	Prospective Controlled	IIB	Gr1= 38 resistant FESS CRS Gr2= 10 FESS success Gr3= 20 healthy controls F/M (Gr1-3): 21/17-6/4-10/10 Age (Gr1-3): 54-42--38 yo	CRS: symptoms despite medical & surgical treatments & positive endoscopy findings. LPR: hypopharyngeal/nasopharyngeal acid event.	History of GERD/LPR (Gr1) Reflux Symptom Questionnaire Sinusitis Score & SNOT-20 Endoscopic score Reflux area index pH<4 Nasopharynx (N) pH<5 Nasopharynx (N) GERD (pH testing)	N=16/38 Gr1-2>Gr3 Gr1-2>Gr3 Gr1-2>Gr3 Gr1-2: 58%; Gr3: 21%; S Gr1-2: 39%; Gr3: 7%; S Gr1-2: 74%; Gr3: 38%; S Gr1-2: 66%; Gr3: 31%; S	1. Patients with recalcitrant CRS post-FESS reported higher number of nasopharyngeal, pharyngeal and esophageal acid reflux events than controls.
Dinis (22) Portugal 2006	Prospective Controlled	IIB	Gr1= 15 resistant CRS Gr2= 5 healthy controls F/M (Gr1,2): 4/11 - 4/1 Age (Gr1,2): 50 yo - 38 yo	CRS: symptoms despite medical treatments & positive CT-scan diagnosis confirmation. LPR: detection of H. Pylori and pepsin in sinonasal tissue.	Helicobacter Pylori Pepsin (serum & tissues) Pepsinogen I (serum & tissues)	Gr1=Gr2 Gr1=Gr2 Gr1=Gr2	1. CRS patients did not have higher H. Pylori and pepsin presence in mucosa tissues than healthy individuals. 2. Older patients had significant higher pepsin/pepsinogen I tissue concentrations.
Wise (23) 2006 USA	Prospective Controlled	IIB	Gr1= 38 resistant FESS CRS Gr2= 10 FESS success Gr3= 20 healthy controls F/M (Gr1-3): 21/17-6/4-10/10 Age (Gr1-3): 54-42--38 yo	CRS: symptoms despite medical & surgical treatments & positive endoscopy findings. LPR: hypopharyngeal/nasopharyngeal acid event.	Correlation analysis modified RSI* & SNOT-20 Patients with vs without pH<5 in nasopharyngeal pH testing Postnasal drip severity *postnasal drip item	S With > without	1. Objective nasopharyngeal findings of acid reflux exist in patients with post-nasal drip symptoms and CRS.
Pincus (24) 2006 USA	Prospective Uncontrolled	IV	N=30 resistant CRS F/M: 23/7 Age: 44 yo	CRS: symptoms despite medical & surgical treatments & positive endoscopy & CT-scan. LPR: nasopharyngeal acid event.	Triple probe pH study (GERD) Nasopharyngeal acid event Treatment efficacy (N=15)* *at least one improved symptom	N=25/30 N=2/30 N=14/15 - N=7 resolution	1. 83% of recalcitrant CRS patients had GERD at the pH study; 6.7% of patients having nasopharyngeal acid event. PPIs may decrease symptoms of CRS and LPR.
Ozmen (25) Turkey 2008	Prospective Controlled	IIB	Gr1= 33 resistant CRS Gr2= 20 healthy controls F/M (Gr1,2): 7/26 - 9/11 Age (Gr1,2): 39 yo - 33 yo	CRS: 3-month symptoms despite medical treatments & positive CT-scan diagnosis confirmation. LPR: hypopharyngeal acid event.	Pharyngeal acid reflux event Nasal lavage pepsin Nasal pepsin SE & SP Correlation: LPR event-pepsin	Gr1: 29/33; Gr2: 11/20; S Gr1: 27/33; Gr2: 10/20; S 100% - 92% S	recalcitrant CRS patients had higher number of acid pharyngeal events and nasal pepsin concentration than healthy individuals. Pepsin & pH events were correlated.

References	Design	EL	Patients characteristics	CRS/LPR Diagnosis	Outcomes	Results (better values)	Findings
Zelenik (26) Czech Republic 2016	Prospective Uncontrolled	IV	Gr1=64 <10-y CRSwNP/CRSnNP Gr2= 17 11-20-y CRSwNP/CRSnNP Gr2= 17 >20-y CRSwNP/CRSnNP F/M (Gr1-3): 31/33-8/9-4/5 Age (Gr1-3): 42-58-61 yo	CRS: 2-y symptoms despite medical or surgical treatments & positive CT-scan (EPOS criteria).	Upright Ryan score & RSI	Gr3>Gr2>Gr1	CRS patients treated for >10 y and those who had >2 FESS had significant LPR at the oropharyngeal pH monitoring.
Ren (27) China 2016	Prospective Controlled	IIB	Gr1= 17 CRSwNP(A)/15 CRSnNP(B) Gr2= 10 healthy controls F/M: 19/23 Age: 41 yo	CRS: symptoms despite medical treatments, position endoscopy & CT-scan (EPOS 2012 criteria). LPR: pepsin A in nasal secretions.	Pepsin A (nasal secretions) MUC5AC, MUC5B, MUC8 MUC4	Gr1A,B>Gr2 Gr1B>Gr1A & Gr2 Gr1A,B=Gr2	Patients with CRSw/nNP had higher proportion of pepsin A in nasal secretions, which was not produced by nasal mucosa.
Wang (28) China 2017	Prospective Controlled	IIB	Gr1= 26 CRSwNP(A)/23 CRSnNP(B) Gr2= 9 healthy controls F/M: 27/31 Age: 39 yo	CRS: symptoms despite medical treatments, position endoscopy & CT-scan (EPOS 2012 criteria). LPR: pepsin A in nasal secretions.	Pepsin A (nasal secretions) Heat shock protein 70	Gr1A,B>Gr2 Gr1A,B>Gr2; Gr1B>Gr1A	CRSw/nNP patients had a higher nasal pepsin A & tissue heat shock protein than healthy controls, which supported a role of pepsin A in mucosa injury of CRS.
Anzic (16) Croatia 2018	RCT	IB	N=60 CRS & LPR Gr1=33 & Gr2 (placebo)=27 F/M: 28/32 Age: 49 yo	CRS: medical history & nasal endoscopy (EPOS guidelines) LPR: symptoms, signs & pharyngeal acid event at the triple probe pH monitoring.	Reduction of: RSI & RFS CRS clinical score Nasal endoscopy findings Eosinophil cationic protein (nasal)	Gr1> Gr2 Gr1> Gr2 Gr1> Gr2 Gr1> Gr2 Gr1= Gr2	PPIs significantly improved reflux and CRS symptoms in patients with recalcitrant CRS.
Brown (29) USA 2020	Retrospective	IV	Gr1=36 CRSn/wNP Gr2= 60 suspected LPR Gr3= 42 CRS & suspected LPR F/M: NP Age: NP	CRS: 3-month CRS symptoms & positive endoscopy or CT-scan LPR: RSI≥13	SNOT-22 total score Sleep, nasal, otologic SNOT-22 Emotional SNOT-22 RSI Correlation: RSI - SNOT-22	Gr3>Gr1; Gr2>Gr1 Gr3>Gr1; Gr2>Gr1 Gr2>Gr1 Gr3>Gr1; Gr2>Gr1 S	Patients with CRS and suspected LPR had higher RSI and SNOT-22 score than those with CRS or suspected LPR only. Suspected LPR patients had no endoscopic CRS findings although high SNOT-22.

References	Design	EL	Patients characteristics	CRS/LPR Diagnosis	Outcomes	Results (better values)	Findings
Lechien (8) Belgium 2021	Prospective Uncontrolled	IV	N=37 CRS F/M: 20/17 Age: 43 yo	CRS: 3-month CRS symptoms & positive endoscopy & CT-scan (EPOS guidelines) LPR: GI endoscopy.	GERD prevalence (esophagitis) Helicobacter Pylori	N=20/22 N=9/22	GERD was prevalent in patients with CRS. GERD symptoms were predictive of recurrence of CRS and the need of FESS.
Yeo (30) Korea 2022	Retrospective	IV	N= 91 CRSn/wNP F/M: 28/63 Age: 50 yo	CRS: symptoms despite medical treatments, position endoscopy & CT-scan. LPR: RSI>12 & RFS>7	Baseline RSI>12 & RFS>7 RSI, RFS, SNOT-22 Correlations: RSI - SNOT-22 pre-RSI & post-SNOT-22	N=58 pre > post FESS S S	Symptoms of LPR and CRS are correlated. Precisely, baseline RSI is associated with post FESS SNOT-22. FESS reduced LPR symptoms.

Table 1 footnotes: Abbreviations: 1/d=once daily; 1/w=once weekly; CRSn/wNP=chronic rhinosinusitis without/with nasal polyps; EPOS=European Position Paper on Rhinosinusitus; FESS=functional endoscopic sinus surgery; GERD=gastroesophageal reflux disease; HP=Helicobacter Pylori; LPR=laryngopharyngeal reflux; MII-pH=multichannel intraluminal impedance pH monitoring; PPIs=proton pump inhibitors; QOLRAD:Quality of Life in Reflux and Dyspepsia; RCT=randomized controlled trial; RSI=reflux symptom index; RSOM-31=Rhinosinusitis outcome measure-31; S=significant; SE=sensitivity; SNOT-20=sinonasal outcome test-20; SP=specificity.

Table 2: Inclusion and exclusion criteria of study populations.

References	Accepted criteria	Exclusion criteria	Control group inclusion criteria
Ulualp (17,18)	N.P.	N.P.	No esophageal/laryngeal/nasal symptoms Normal transnasal esophagoscopy
DiBaise (19)	Smoker	Gastric/esophageal surgery Antiacid treatment	-
Wong (20)	N.P.	N.P.	-
Jecker (21)	N.P.	N.P.	No history of CRS, GERD, heartburn, belching; non-smoker; no medication. Normal nasal endoscopy.
DelGaudio (4) Wise (23)	Smoker, allergic/allergic CRS, current/history of reflux, Nissen surgery, Fungal CRS	N.P.	No history of CRS.
Dinis (22)	Allergic & asthmatic	Cystic fibrosis, immotile cilia syndrome & immunodeficiencies.	Symptomatic concha bullosa without inflammation (imaging).
Pincus (24)	N.P.	Allergic, asthmatic, ciliary or immune disorders, gastrointestinal disorders.	-
Ozmen (25)	N.P.	Samter syndrome Antireflux therapy.	Symptomatic concha bullosa or septum deviation, no inflammation (imaging)
Zelenik (26)	N.P.	Cystic fibrosis, immotile cilia, fungal disease, vasculitis, cancer, immune or granulomatous disorders, and smoker.	-
Ren (27) Wang (28)	N.P.	Cystic fibrosis, immotile cilia, allergic, fungal diseases, immune disorders, antireflux therapy.	Symptomatic concha bullosa without inflammation (imaging).
Anzic (16)	N.P.	Cystic fibrosis, allergic, severe systemic disease and asthmatic.	-
Brown (29)	N.P.	Sinonasal cancer, radiation, immune or granulomatous diseases.	-
Lechien (8)	N.P.	Cystic fibrosis, immotile cilia, smoker, immune disorder, fungal or allergic CRS, polyposis, pregnant.	-
Yeo (30)	Smoker, allergic or allergic CRS	Allergic, fungal diseases, retention cysts, mucocele, tumor, medical or surgical antireflux treatments.	-

Table 2 footnotes: Abbreviations: GERD=gastroesophageal reflux disease; LPR=laryngopharyngeal reflux; NP=not provided; RAI=reflux area index; RFS=reflux finding score; RSI=reflux symptom index; UES=upper esophageal sphincter; UHC=Immunohistochemical staining.

Table 3: Reflux diagnostic criteria.

References	Diagnosis tools	Diagnosis criteria
Ulualp (17,18)	Triple-probe pH study: esophageal (2), hypopharyngeal (1) sensors.	Simultaneous decrease of pH<4 in 3 sensor sites (low, upper esophageal and pharyngeal). Meals: standardized, low acid. Antireflux therapy: N.P.
DiBaise (19)	Dual-probe pH study: esophageal (2) sensors.	Simultaneous decrease of pH<4 in 2 sensor sites (low & upper esophageal). Meals: N.P. Antireflux therapy: no.
Wong (20)	Four-probe pH study: esophageal (2), hypopharyngeal (2) sensors.	Reflux index>7%. pH event = pH>4, >4s (distal sensor). Meals: low acid foods and beverages. Antireflux therapy: 2-5-day stop.
Jecker (21)	Dual-probe pH study: esophageal & hypopharyngeal sensors.	Simultaneous decrease of pH≤4 in 2 sensor sites (esophageal and pharyngeal). Meals: N.P. Antireflux therapy: N.P.
DelGaudio (4) Wise (23)	Triple-probe pH study: esophageal (1), UES (1), nasopharyngeal (1) sensors.	Simultaneous decrease of pH<4 in 3 sensor sites (esophageal, UES & nasopharyngeal (pH<5)). LPR: UES: RAI score> 6.3 or >6.9 events. Meals: N.P. Antireflux therapy: 1-week stop.
Dinis (22)	Pepsin detection in sinonasal tissue.	Radioimmunoassay; positive >1 μg/mL pepsin Meals & antireflux therapy: N.P.
Pincus (24)	Triple-probe pH study: esophageal (2), nasopharyngeal (1) sensors.	Simultaneous decrease of pH<4 in 2 sensor sites: esophageal and nasopharyngeal. Meals: N.P. Antireflux therapy: no.
Ozmen (25)	Dual-probe pH study: esophageal & hypopharyngeal sensors.	Simultaneous decrease of pH≤4 in 2 sensor sites (esophageal and pharyngeal). Meals: N.P. Antireflux therapy: N.P.
Zelenik (26)	Oropharyngeal pH testing: oropharyngeal sensor (1).	Ryan score: upright>9.4, supine>6.8 Meals: N.P. Antireflux therapy: N.P.
Ren (27) Wang (28)	Pepsin detection in nasal secretions (3mL saline solution washing), tissues, blood plasma.	IHC, Western blot & ELISA Meals: N.P. Antireflux therapy: no.
Anzic (16)	Triple-probe pH study: esophageal (2), hypopharyngeal (1) sensors	Reflux area index (pH=4) >6.3/(pH=5) >72.5. Meals: N.P. Antireflux therapy: N.P.
Lechien (8)	Gastrointestinal endoscopy	Esophagitis
Brown (29)	Symptoms.	RSI≥13
Yeo (30)	Symptoms & signs.	RSI>12 & RFS>7

Table 3 footnotes: Abbreviations: UHC=Immunohistochemical staining; NP=not provided; RAI=reflux area index; RFS=reflux finding score; RSI=reflux symptom index; UES=upper esophageal sphincter

Figure 1: Chart flow.

Figure 1 footnotes: -.

Appendix 1 Bias analysis.

References	Diagnosis disorder accuracy CRS	LPR	Confounding factors	Association outcomes
Ulualp (17,18)	Yes	Probably yes	N.P.	Probably no
DiBaise (19)	Probably yes	Probably no	Probably no	No
Wong (20)	Probably yes	Probably yes	N.P.	Probably yes
Jecker (21)	Yes	Probably yes	N.P.	Probably no
DelGaudio (4)	Probably yes	Probably yes	Probably no	Probably yes
Wise (23)	Probably yes	Probably yes	Probably no	Probably yes
Dinis (22)	Yes	Probably yes	Probably yes	Probably yes
Pincus (24)	Yes	Probably yes	Probably no	Probably yes
Ozmen (25)	Yes	Probably yes	No	Probably yes
Zelenik (26)	Yes	Probably yes	Probably yes	Probably no
Ren (27)	Yes	Probably yes	Probably yes	Probably yes
Wang (28)	Yes	Probably yes	Probably yes	Probably yes
Anzic (16)	Probably yes	Probably yes	No	No
Brown (29)	Probably yes	No	No	No
Lechien (8)	Yes	Probably no	Yes	No
Yeo (30)	Yes	No	No	No

Appendix 1 footnotes: According to the bias tool used, the following points were considered: CRS diagnosis: yes=association of symptoms, findings and CT-scan; probably yes=association of symptoms and findings; probably no=symptoms or findings. LPR diagnosis: yes=hypopharyngeal-esophageal impedance pH monitoring considering acid/nonacid pharyngeal reflux episodes; probably yes=hypopharyngeal-esophageal pH monitoring considering acid reflux events or esophageal impedance-pH monitoring or pepsin detection in nasal tissues or secretions; probably no=Esophageal dual probe or esophageal single probe pH monitoring or esophagitis; No=symptoms and/or signs. Authors considered the exclusion of main confounding factors for both CRS and reflux (i.e. tobacco; allergic RS; fungal RS; cystic fibrosis; immunodeficiency disorder; ciliary dyskinesia syndrome): Yes=6/6; Probably yes=4,5/6; probably no=3,4/6; no=0-2/6. Outcomes of association: yes=the methods allowed the objective detection of all types of reflux in nasopharyngeal/nasal region; probably yes=the methods allowed the objective detection of some types of reflux in nasopharyngeal/nasal region; probably no=the methods allowed the objective indirect

detection of reflux in esophageal or pharyngeal region; no=the method only allowed the suspicion of reflux in patients.