ABSTRACT

for the doctoral dissertation of Kalamkas Tulendinovna Sagandykova

on the topic:

"Clinical and Functional Assessment of the Impact of Gastroesophageal Reflux Disease on the Development and Course of Chronic Nasal and Nasopharyngeal Pathology"

submitted for the degree of Doctor (PhD) in the specialty 8D10102 – Medicine

Relevance of the Research Topic:

Chronic rhinosinusitis (CRS) is one of the most common forms of inflammatory diseases of the upper respiratory tract and represents a significant medical and social problem due to its recurrent course, pronounced reduction in patients' quality of life, and high resistance to standard therapy. The global overall prevalence of CRS and CRS with nasal polyps has been reported at 8.71% [1].

Despite advances in diagnostic methods and improvements in therapeutic approaches, a substantial proportion of patients continue to exhibit refractory CRS [2].

In recent years, attention has increasingly focused on the role of extraesophageal manifestations of gastroesophageal reflux, including laryngopharyngeal reflux (LPR), in the pathogenesis of chronic otorhinolaryngological disorders. In addition, the potential involvement of *Helicobacter pylori* as a cofactor in the chronic inflammatory process of the nasopharynx has been discussed [3].

The lack of objective, clinically reproducible diagnostic criteria that reliably assess the impact of gastroesophageal and laryngopharyngeal reflux on the course of CRS complicates the selection of effective personalized therapy. In this context, studying the clinical and functional characteristics of CRS in the presence of gastroesophageal pathology, as well as the development and validation of diagnostic and prognostic approaches, represents a pressing task in modern otorhinolaryngology.

Aim of the Dissertation Research:

To optimize the diagnosis and personalized management of patients with reflux-associated chronic rhinosinusitis through a comprehensive assessment of the clinical and endoscopic features of the disease and the development of standardized diagnostic criteria.

Study objectives:

1. To analyze the prevalence of *Helicobacter pylori* in patients with chronic rhinosinusitis and to identify its relationship with the clinical and morphological characteristics of the disease.
2. To identify specific clinical and endoscopic features of chronic rhinosinusitis associated with gastroesophageal and laryngopharyngeal reflux.
3. To develop and validate an endoscopic scoring system for assessing reflux-associated changes in the mucosa of the nasal cavity and nasopharynx.
4. To determine the sensitivity of the developed diagnostic scale to changes in endoscopic findings and clinical symptoms of chronic rhinosinusitis during anti-reflux therapy.
5. To develop and implement a diagnostic and treatment algorithm for patients with chronic rhinosinusitis associated with laryngopharyngeal and gastroesophageal reflux.

Research Methods

The study was conducted in stages and included a systematic literature review, a clinical cross-sectional study, validation of the developed endoscopic scale NRES (Nasopharyngeal Reflux Endoscopic Score), and testing of a diagnostic algorithm.

In accordance with international PRISMA guidelines, a systematic review was conducted to investigate the prevalence and clinical significance of Helicobacter pylori in patients with chronic

rhinosinusitis (CRS), both with and without nasal polyps, as well as its association with gastroesophageal pathology, including laryngopharyngeal reflux.

The search was performed in PubMed, Scopus, and Cochrane Library databases from January 1990 to September 2024 using keywords such as Helicobacter pylori, chronic rhinosinusitis, nasal polyps, reflux, GERD, LPR, pepsin, PCR, IHC, etc. Both prospective and retrospective studies were included if they verified H. pylori in nasal/nasopharyngeal tissues and assessed reflux symptoms. Out of 42 publications identified, 20 met the inclusion criteria, covering more than 1,100 patients with CRS and healthy individuals. Diagnostic methods included PCR, immunohistochemistry, urease and breath tests, ELISA, and gastric biopsy.

The second stage was a cross-sectional observational study, conducted from September 2023 to February 2024 at the Diagnostic Center and Multidisciplinary City Hospital No. 1 in Astana, examining 521 adult patients with CRS. The main group included 95 patients with chronic rhinosinusitis and pronounced reflux symptoms, assessed using validated questionnaires: the Reflux Symptom Index (RSI; Belafsky et al., 2002) and the Reflux Symptom Score-12 (RSS-12; Lechien et al., 2019). The control consisted of two groups: 41 patients with CRS without signs of LPR and 10 healthy volunteers.

Inclusion criteria: age >18 years; diagnosis of CRS (EPOS 2020); presence of laryngeal endoscopy – RFS, nasal and nasopharyngeal endoscopy with photo/video documentation; completed RSI and RSS-12 questionnaires; informed consent.

Exclusion criteria: acute ENT diseases; previous ENT surgeries; severe comorbidities; pregnancy or lactation; refusal to participate.

All patients underwent endoscopy of the nasal cavity and nasopharynx (assessed using the Camacho endoscopic scale), laryngeal endoscopy (Reflux Finding Score [RFS] for objective assessment of laryngopharyngeal reflux signs), esophagogastroduodenoscopy, esophageal pH-metry, and completed validated questionnaires (RSI and RSS-12).

The next stage involved developing the diagnostic endoscopic scale and assessing its accuracy through a prospective cohort study at two centers in Astana from September 2023 to February 2025. A total of 216 patients were included, divided into three groups:

CRS with signs of LPR (n=116)

CRS without LPR (n=69)

Healthy individuals (n=31)

LPR diagnostic criteria: combined RSI and RSS score >13, clinical data, and endoscopic findings with H. pylori detection.

Methods: All patients underwent nasal and nasopharyngeal endoscopy and assessment using NRES, Lund–Kennedy (L-K; Lund & Kennedy, 1995), RFS, RSI, and RSS at baseline and during follow-up at 6 and 12 months. Patients with LPR received anti-reflux therapy with repeat endoscopic monitoring.

Statistical analyses were performed using SPSS 26.0 and R 4.3.0, including descriptive statistics, ROC analysis, Wilcoxon test, Spearman and Pearson correlation coefficients, and regression analysis. The diagnostic accuracy of NRES was evaluated in terms of sensitivity, specificity, AUC, and confidence intervals.

The final stage of the study involved the development and implementation of a diagnostic algorithm for managing patients with reflux-associated chronic rhinosinusitis.

All study stages were approved by the local bioethics committee (protocols No. 13 dated 29.11.2023 and No. 2 dated 26.05.2025).

Object of the Study

The objects of the study were patients with various forms of chronic rhinosinusitis (CRS), including those exhibiting signs of gastroesophageal and laryngopharyngeal reflux.

Subject of the Study

The subject of the study included the clinical-functional and endoscopic characteristics of CRS in patients with concomitant gastroesophageal pathology; the prevalence and significance of

Helicobacter pylori; validation of the endoscopic assessment scale; and evaluation of the effectiveness of the developed diagnostic algorithm and therapy based on the analysis of reflux-associated changes.

Key Points Submitted for Defense

1. The developed diagnostic scale, Nasopharyngeal Reflux Endoscopic Score (NRES), demonstrates high sensitivity (98%) and specificity (96%) and is simple to apply, allowing for an objective assessment of reflux-associated changes in the posterior regions of the nasal cavity and nasopharynx in both outpatient and ENT hospital settings.
2. The high clinical relevance of the NRES scale for dynamic monitoring of patients undergoing anti-reflux therapy has been demonstrated, enabling objective evaluation of treatment effectiveness and the development of individualized management plans.
3. Diagnostic and prognostic markers for the course of CRS in the context of gastroesophageal pathology—such as characteristic clinical-endoscopic signs, presence of *Helicobacter pylori* infection, and elevated NRES scores—allow general practitioners and otorhinolaryngologists to personalize patient management.
4. The proposed diagnostic algorithm, based on comprehensive clinical-functional assessment and consideration of reflux-associated factors, is recommended for implementation in clinical practice to improve diagnostic accuracy and therapeutic outcomes in patients with chronic rhinosinusitis.

Description of the Main Results of the Study

To achieve the research objectives, a comprehensive research program was developed and implemented, which included the following stages:

1. Systematic Literature Review

Main results of the review:

- The prevalence of *H. pylori* in polyp tissue in CRS patients ranged from 32.7% to 37.1%, compared to 3.6%–14.8% in healthy individuals.
- The presence of *H. pylori* was more frequently associated with signs of gastroesophageal and laryngopharyngeal reflux.
- A pathogenetic link was identified between *H. pylori*, reflux pathology, and the chronicity of inflammation in CRS.
- The necessity of identifying a subgroup of CRS patients with gastroesophageal dysfunction was substantiated to enable individualized treatment approaches.

2. Results of the Cross-Sectional Observational Study

Objective: To assess the frequency and nature of specific endoscopic signs of CRS in patients with symptoms of gastroesophageal and laryngopharyngeal reflux.

In patients of the main study group, the following characteristic endoscopic signs were observed:

- Hypertrophy of the posterior end of the inferior nasal turbinate – 84%;
- Pronounced vascular pattern of the nasopharyngeal mucosa – 95.7%;
- Hyperemia and swelling of the nasopharyngeal vault – 87.4%;
- Accumulation of viscous mucus – 81.1%;
- Asymmetry of the oropharyngeal mucosa – 65.3%.

A correlation was established between the severity of symptoms, the endoscopic findings, and the likelihood of reflux.

3. Development and Validation of the NRES Scale

Objective: To create an objective endoscopic scale, the Nasopharyngeal Reflux Endoscopic Score (NRES), for the diagnosis of reflux-associated changes in the nasal cavity and nasopharyngeal mucosa in CRS patients.

Characteristics of NRES:

- Includes 10 endoscopic signs (edema, mucus, hyperemia, hypertrophy, etc.);
- Three-point scale for each sign (0–2);

- Total score range: 0–20 points.

Table 1. "Nasopharyngeal Reflux Endoscopic Score (NRES)"

Signs of Nasopharyngeal Reflux Exposure	0(Absent)	1(Moderately Expressed)	2(Severely Expressed)
Nose			
Asymmetry between the anterior and posterior regions of the nasal cavity	☐	☐	☐
Predominantly unilateral hypertrophy of the posterior end of the inferior turbinate	☐	☐	☐
Absence of mucus in the middle nasal passage	☐	☐	☐
Nasopharynx			
Hypertrophy of the posterior wall of the nasopharynx	☐	☐	☐
Hypertrophy of the Eustachian tube opening	☐	☐	☐
Increased vascular pattern	☐	☐	☐
Presence of mucus	☐	☐	☐
Erythema or inflammation of the nasopharyngeal mucosa	☐	☐	☐
Atrophic changes in the mucosa	☐	☐	☐
Presence of granulations or fibrotic changes	☐	☐	☐

Statistical Analysis: ROC analysis, Wilcoxon test, correlation and regression analyses.
Main Results:

- Mean NRES scores: CRS + LPR – 11.59; CRS without LPR – 3.10; Control – 2.16 ($p < 0.001$).
- ROC analysis (cut-off ≥ 8.5): AUC = 0.998; sensitivity – 98%, specificity – 96%, PPV/NPV – 97% each.
- NRES showed strong correlation with RSS ($r = 0.768$), RSI ($r = 0.766$), RFS ($r = 0.769$), and weak correlation with L-K ($r = 0.221$).
- Gender, age, and endoscopic classification did not significantly affect NRES values ($p > 0.05$).
- In the CRS + LPR group (n = 116), a significant reduction in NRES, RSI, and RSS scores was observed at 6 and 12 months of therapy, confirming the scale's sensitivity to treatment and its applicability for monitoring patient progress.

4. Results of the Diagnostic Algorithm Development
Objective of this stage: To create a structured management pathway for patients with CRS associated with LPR and *Helicobacter pylori*.
Based on the data from the systematic review, clinical study, and NRES validation results, a diagnostic and management algorithm was proposed, including the following stages (Figure 1):

Pilot Testing of the Algorithm

The implementation of the algorithm at the State Communal Enterprise on the Right of Economic Management "City Polyclinic No. 11" (Astana) demonstrated:

- Increased diagnostic accuracy;
- Timely initiation of etiopathogenetic therapy;
- Objective assessment of therapy effectiveness over time.

Scientific Novelty Justification

Within the framework of this study:

- For the first time, a comprehensive clinical-functional study of chronic rhinosinusitis (CRS) was conducted in patients with concomitant gastroesophageal pathology, including manifestations of gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR). Specific clinical-endoscopic features were identified that allow the recognition of reflux-associated forms of the disease, characterized by pronounced symptoms, morphological changes in the mucosa of the nasal cavity and nasopharynx, and a tendency for recurrent course.
- An original endoscopic assessment scale, the Nasopharyngeal Reflux Endoscopic Score (NRES), was developed and validated for objective diagnosis and dynamic monitoring of patients with CRS associated with LPR.
- A high degree of correlation was established between NRES scores and widely used symptom scales (RSI, RSS, RFS), confirming its clinical utility in differential diagnosis and predicting therapeutic efficacy.
- For the first time, the sensitivity of NRES to mucosal changes during anti-reflux therapy was demonstrated, making it a useful tool for monitoring treatment outcomes in reflux-induced CRS.
- A structured diagnostic algorithm for managing CRS patients was proposed for the first time, which accounts for LPR symptoms and *Helicobacter pylori* infection as potential triggers and modifiers of the inflammatory process.

Practical Significance of the Results

- The diagnostic scale developed in this study, NRES, is simple, reproducible, and sensitive for the objective assessment of reflux-associated changes in the nasal cavity and nasopharynx. It can be applied in both outpatient and inpatient settings.
- Diagnostic and prognostic markers of CRS course in the context of gastroesophageal pathology were established, including typical clinical-endoscopic features, presence of *H. pylori*, and elevated NRES scores, enabling personalized treatment approaches.
- The data support the inclusion of RSI, RSS questionnaires, and the NRES endoscopic scale in routine screening of CRS patients, particularly in cases of standard therapy failure, improving detection of subclinical LPR and guiding treatment adjustments.
- The effectiveness of NRES for dynamic monitoring of patients undergoing anti-reflux therapy was confirmed, allowing clinicians, including general practitioners and otorhinolaryngologists, to evaluate treatment outcomes and develop individualized management plans.
- The structured diagnostic algorithm proposed in the study can be recommended for clinical practice to optimize diagnosis and improve therapeutic outcomes for patients with CRS.

Personal Contribution of the Doctoral Candidate

The author's personal contribution includes the development of the theoretical and methodological framework of the study, formulation of its aims and objectives, organization and conduct of the research, direct participation in all research stages, statistical data analysis, writing of publications, interpretation and discussion of results, formulation of defendable statements, and development of conclusions and practical recommendations.

Conclusions

Chronic rhinosinusitis (CRS) associated with extraesophageal manifestations of gastroesophageal reflux disease (GERD) represents a clinically and functionally distinct phenotype. It is

characterized by pronounced symptoms, a recurrent course, reduced responsiveness to standard therapy, and typical endoscopic features, including hypertrophy of the posterior parts of the nasal turbinates, edema and hyperemia of the nasopharyngeal mucosa, and accumulation of viscous mucus.

A significant proportion of CRS patients (32.7–37.1%) exhibit Helicobacter pylori infection and symptoms of laryngopharyngeal reflux (LPR), especially in cases with nasal polyps. This supports the potential role of H. pylori as a cofactor in chronic inflammation and justifies its inclusion in diagnostic algorithms to enable personalized treatment strategies.

The developed Nasopharyngeal Reflux Endoscopic Score (NRES) is a validated and clinically significant tool for diagnosing and monitoring reflux-associated changes in the nasal cavity and nasopharynx. It demonstrated high sensitivity (98%) and specificity (96%), correlates with the RSI, RSS, and RFS questionnaires, and can be applied both for primary diagnosis and for dynamic monitoring following anti-reflux therapy.

The proposed diagnostic algorithm improves the accuracy of diagnosis and evaluation of therapy effectiveness in patients with CRS associated with gastroesophageal pathology.

Based on comprehensive analysis of clinical, endoscopic, and instrumental data, a diagnostic and treatment algorithm for patients with reflux-associated CRS was developed. Its clinical pilot implementation optimized patient routing, increased diagnostic accuracy, and enhanced treatment effectiveness. The results have been incorporated into practice at the State Communal Enterprise on the Right of Economic Management "City Polyclinic No. 11," Astana, as confirmed by the corresponding implementation act.

Dissertation Results Testing (Pilot Implementation)

The results of the study and the main provisions of the dissertation were presented and discussed at the following international scientific and practical conferences:

13th Balkan Congress of Otorhinolaryngology - Head and Neck Surgery / 3rd Congress of Central and West Asian ORL HNS Association, 6–8 June 2024, Istanbul, Turkey;

The First Eurasian International School of Young Otorhinolaryngologists, dedicated to Professor Marius Stefanovich Pluzhnikov, 3–4 June 2024, Astana, Kazakhstan;

National Congress with international participation: "New Innovative Technologies in Otorhinolaryngology and Head & Neck Surgery," dedicated to the 180th anniversary of Abai Kunanbayev, Semey, Kazakhstan;

The 46th Turkish National Congress of Otorhinolaryngology and Head & Neck Surgery, 5–9 November 2025, Turkish Republic of Northern Cyprus.

Publications Related to the Dissertation

A total of nine scientific publications have been produced based on the dissertation, including:

Three full-text articles in journals indexed in Scopus and Web of Science: European Archives of Oto-Rhino-Laryngology (impact factor 1.9, CiteScore 5.3, 89th percentile), Medicina (impact factor 2.4, CiteScore 3.3, 75th percentile), Journal of Clinical Medicine (impact factor 2.9, CiteScore 5.2, 86th percentile);

One article in journals recommended by the Committee for Quality Assurance in Science and Higher Education, Ministry of Science and Higher Education of the Republic of Kazakhstan;

Five abstracts in international conference proceedings.

Implementation of Research Results

State Communal Enterprise on the Right of Economic Management "City Polyclinic No. 11," Astana — Algorithm for Diagnosis and Treatment of Reflux-Associated Chronic Rhinosinusitis, Patent No. 56818, 15 April 2025;

Features of Chronic Rhinosinusitis Associated with Gastroesophageal Reflux Disease, Patent No. 56819, 15 April 2025;

Features of Clinical Manifestations of Otolaryngological Diseases Caused by Gastroesophageal Reflux Disease, Patent No. 56820, 15 April 2025;

Clinical-Functional Assessment of the Impact of Gastroesophageal Reflux Disease on the Development and Course of Chronic Nasal and Nasopharyngeal Pathology, Patent No. 57490, 5 May 2025;
Validation of the Nasopharyngeal Reflux Endoscopic Score (NRES) for reflux-induced chronic rhinosinusitis.

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