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REVIEW ARTICLE

Association between *Helicobacter pylori*, reflux and chronic rhinosinusitis: a systematic review

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Abstract

Background The prevalence, role, and clinical relevance of Helicobacter Pylori (HP) in sinonasal tissues of patients with chronic rhinosinusitis remain unclear.

Objective To investigate the prevalence and clinical relevance of Helicobacter Pylori (HP) in chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and without nasal polyps (CRSSNP).

Methods Three investigators conducted a PubMed, Scopus, and Cochrane Library systematic review of the prevalence and clinical relevance of HP infection in CRS patients through the PRISMA framework. A bias analysis was conducted to identify potential heterogeneity and biases across studies.

Results Of the 42 identified studies, 20 met the inclusion criteria, accounting for 741 CRS patients and 368 controls. HP was detected in 37.1% (n = 127/342) of polyps of CRSwNP patients with the polymerase chain reaction (PCR) and 32.7% (n = 37/113) of polyp tissue with the immunohistochemistry (IHC). Controls reported a nasal PCR and IHC detection rates of 14.8% (n = 36/243) and 3.6% (n = 3/84), respectively. The HP rate did not differ between CRSwNP and CRSsNP. Among patients with CRS, the enzyme-linked immunosorbent assay testing detected blood HP antigens in 48.7% (n = 74/152) of CRS patients and 41.6% (n = 37/89) of controls. The detection of HP in polyps was associated with the severity of gastroesophageal reflux disease (GERD). There was an important heterogeneity between studies for the inclusion criteria, methods of HP detection, and reflux outcomes.

Conclusion Helicobacter Pylori can be detected in one-third of sinonasal tissues from patients with CRS and can be considered a biomarker of GERD. The potential role of HP in the development of CRS remains unclear. The heterogeneity between studies limits the drawing of valid conclusions.

Keywords Chronic Rhinosinusitis · Otolaryngology · Otorhinolaryngology · Laryngopharyngeal · Gastroesophageal · Reflux · Helicobacter Pylori · Polyp

Introduction

Chronic rhinosinusitis (CRS) represents a significant health issue, ranking as one of the most prevalent chronic disorders in the U.S. and Europe [1]. CRS can be classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSSNP), each with distinct physiological and pathological features [2]. The etiology of CRS is multifactorial, with several contributing factors, including viral infections, asthma, allergies, immune deficiencies, and environmental exposures such as smoking and pollution [3, 4]. Laryngopharyngeal reflux disease (LPRD) has long been identified as a contributing factor of CRS through the deposit of gastroduodenal enzymes in the nasal mucosa, leading to inflammation and meatus obstruction [5]. The refluxate gastroduodenal content in the otolaryngological region may include the common gastroduodenal enzymes (e.g., pepsin bile salts, elastase), cholesterol, and Helicobacter pylori (HP) [6, 7]. Then, H. *pylori* (HP) is suspected to be

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associated with the development and the severity of several otorhinolaryngological conditions, including chronic tonsillitis, chronic otitis media, or LPRD [8–10]. In addition to its potential pathophysiological role, HP could be an indirect biomarker of LPRD.

The objective of this systematic review was to explore the prevalence and clinical relevance of HP in CRS.

Materials and methods

The criteria for study inclusion were based on the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework [11]. Three authors independently reviewed and extracted data according to the PRISMA checklist for systematic reviews and the EQUATOR network reporting guidelines [12].

Type of studies

The authors included uncontrolled, controlled prospective, or retrospective studies investigating the presence of HP in adult patients with CRSwNP or CRSSNP. The studies had to be published between January 1990 and September 2024 in English, Spanish, or French peer-reviewed journals. Case reports were excluded.

Population

The diagnosis of CRS was based on the clinical criteria defined by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [2], involving the evaluation of symptoms, findings, sinus CT-scan, and histological examination (polyps). The study included operated CRS patients or individuals with unoperated CRS and histopathological samples. In patients undergoing functional endoscopic sinus surgery (FESS), the presence of HP was identified in either sinonasal secretions or mucosa samples. In the selected studies, various methods were used for the diagnosis of HP, including enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), gastric biopsy, urease tests (such as the Campilobacter-like organism (CLO) test and CLO broth test), C-urea breath test, modified McMullen test, Giemsa stain, hematoxylin and eosin (H&E) stain, culture, stool antigen test, and immunohistochemistry (IHC).

Among studies investigating reflux diseases, the authors considered the diagnosis of Gastroesophageal reflux disease (GERD) according to the Lyon consensus [13]. GERD consists of grade C or D esophagitis (Los Angeles grading), esophageal stricture, or acid exposure time > 6% of the testing time [13]. The LPRD diagnosis was based on Dubai consensus [13], which suggests the confirmation of the diagnosis for patients with more than one pharyngeal reflux event at the 24-h multichannel intraluminal impedance-pH monitoring (HEMII-pH).

Intervention and comparison

The study included untreated patients or patients undergoing FESS. For controlled studies, the analysis should primarily compare the presence of HP in patients with CRS *versus* healthy individuals (controls).

Outcomes

The following outcomes were reviewed: study design, number of patients, gender ratio, mean age, HP detection, CRS and reflux diagnosis, CRS types, and outcomes. Blood, mucosa, and air detection of HP were considered.

Timing and setting

There were no criteria for specific stages or timing in the 'disease process' of the study population.

Research strategy

The publication search was conducted on PubMed, Embase, and Cochrane Library by three independent investigators (JRL, JK, KR). The database was screened for abstracts and titles referring to the description of data related to the investigation of HP in CRS patients. The findings of the search strategy were reviewed for relevance, and the reference lists of these publications were examined for additional pertinent studies. The following keywords were used in the database with the Boolean operators AND/OR: 'chronic', 'rhinosinusitis', 'Helicobacter pylori', 'nasal polyps', 'reflux', 'gastroesophageal', 'laryngeal', 'laryngopharyngeal', 'pepsin' and 'PCR'. The three investigators analyzed the full texts of the selected publications. The studies were classified according to the Oxford levels of evidence (I-V) and categorized based on their design (prospective or retrospective). Additionally, the authors investigated findings from studies examining the effect of gastroduodenal reflux content on the nasal mucosa. The systematic review was not registered in PROSPERO.

Bias analysis

The bias analysis was carried out by two investigators with the Methodological Index for Non-Randomized Studies (MINORS) tool, which is a validated instrument designed for assessing the quality of non-randomized surgical studies [15]. The MINORS tool consists of 12 items related to the analysis of methodological points of comparative and non-comparative studies. The aim of the study was assessed as clearly stated (2), unclear (1), or absent (0). The inclusion of

patients was judged for clearly reported consecutive inclusion (2), unclear consecutive inclusion (1), or no consecutive inclusion (0). The prospective data collection was evaluated as prospective (2), retrospective analysis of prospective recruited patients (1), or absent (0). The quality of endpoints was considered as high (2) if the authors assessed the outcomes with at least two validated and objective approaches on tissues (ELISA, PCR, Western blot). The use of one method was judged as moderate (1), whereas the HP indirect assessment (only blood biology or breath test) was judged fair (0). For prospective studies investigating treatments, the follow-up period was considered adequate (2) for at least 3 months of HP/reflux treatment. A shorter follow-up was considered less reliable to evaluate accurately the therapeutic effectiveness on HP outcomes. Finally, the 5% rate of patients lost to follow-up patients was considered as the threshold in the MINORS, while the study size calculation needed to be performed (2), mentioned as unnecessary (1), or absent (0). The control group was judged as valid for nasal biopsies from healthy individuals, individuals with traumatic nasal conditions, or concha bullosa without infection. Nasal conditions associated with potential infection or reflux, such as inferior turbinate hypertrophy related to gaseous reflux, or infected concha bullosa, were considered moderately valid (1). The ideal MINORS score was 16 for non-comparative studies and 24 for comparative studies [15].

Results

Of the 42 studies initially identified, 20 met the inclusion criteria for this systematic review (Fig. 1, Table 1) [15–33]. There were 17 controlled [15–26, 29, 31–33] and 3 uncontrolled prospective studies [27, 28, 30], accounting for 741 CRS patients and 368 controls (Table 1). In studies reporting gender information, there were 172 females and 339 males with CRS, respectively. The mean age was 52 years, ranging from 22 to 61 years (Table 1). Most studies (n = 15) focused on the relationship between HP and CRSwNP (Table 1) [16, 19–26, 28–33]. The type of CRS was unspecified in one study [18]. The diagnosis of CRS was mostly based on symptoms, nasofibroscopy findings, and CT scans (Table 1). Among recent studies, the EPOS criteria have been considered in only one study [27].

Helicobacter pylori detection in chronic rhinosinusitis

The methods used for detecting HP in nasal tissues, stomach, or blood are reported in Table 2. Most studies based the HP detection on PCR, urease, or IHC. The polymerase chain reaction (PCR) was used to document HP in 8 studies, including CRSwNP [20–22, 24, 25, 28, 31, 33], and 2 studies investigating CRSsNP patients [15, 17]. Among studies using nasal PCR, HP was detected in 37.1% (n = 127/342) of polyps of CRSwNP patients. The analysis of nasal tissue of controls (patients without CRSwNP or CRSsNP) reported a nasal HP PCR detection rate of 14.8% (n = 36/243). IHC was used in 5 studies for detecting HP in sinonasal tissues [16, 18, 19, 23, 26]. The IHC approach revealed HP in nasal polyps in 32.7% (n = 37/113) of CRSwNP patients and 3.6% (n = 3/84) of controls, respectively. Regardless of the detection method, HP was found in 8.7% to 33% of patients with CRSsNP. As found in Table 1, the prevalence of HP did not differ between CRSwNP and CRSsNP patients. Among patients with CRS, the ELISA testing detected blood HP antigens in 48.7% (n = 74/152) of CRS patients and 41.6% (n = 37/89) of controls (Table 1) [16, 24, 31].

Reflux Diagnosis Criteria

GERD and LPRD were investigated in 6 studies [15, 16, 26–29], and one study [17], respectively. No GERD studies adhered to international consensus for the definition of GERD. Zika et al. observed that all patients with recalcitrant CRSwNP had GERD symptoms [28], while 28 (77.8%) had gastric HP. In another investigation [27], the severity of GERD symptoms was similarly associated with the recurrence of CRSSNP symptoms. In the study of Bansal et al., 7/35 CRSwNP and 6/35 controls reported GERD symptoms, which demonstrated the lack of significant differences across groups [26]. The preliminary study of Ozdek et al. observed that 5/12 CRSwNP patients had GERD symptoms with 3/5 with HP detection in polyps [15]. Among the HP + group, only one patient did not have GERD symptoms. Similarly, Cvorovic et al., reported that 8/23 CRSwNP patients had GERD symptoms, and among them, 6/8 had HP in nasal polyps. The authors of these two studies suggested that HP was exclusively detected in polyps of patients with both CRSwNP and GERD [29]. Dinis et al. investigated the pepsin and pepsinogen in sinonasal tissues of recalcitrant CRSSNP patients and controls without observing significant differences between groups [17].

Bias analysis

The MINORS are reported in Table 3. The inclusion and exclusion criteria used for determining the bias analysis are summarized in Appendix 1. The mean MINORS was 12.2 (standard deviation: 2.3). No study reached the adequate MINORS score. The aim of the study was clearly stated in all publications. No author reported having included consecutive patients. The collection of data was prospective in all studies. Nine teams have considered using more than one method for detecting HP [16, 17, 19, 22, 24, 28, 29, 31, 33], and others using one method

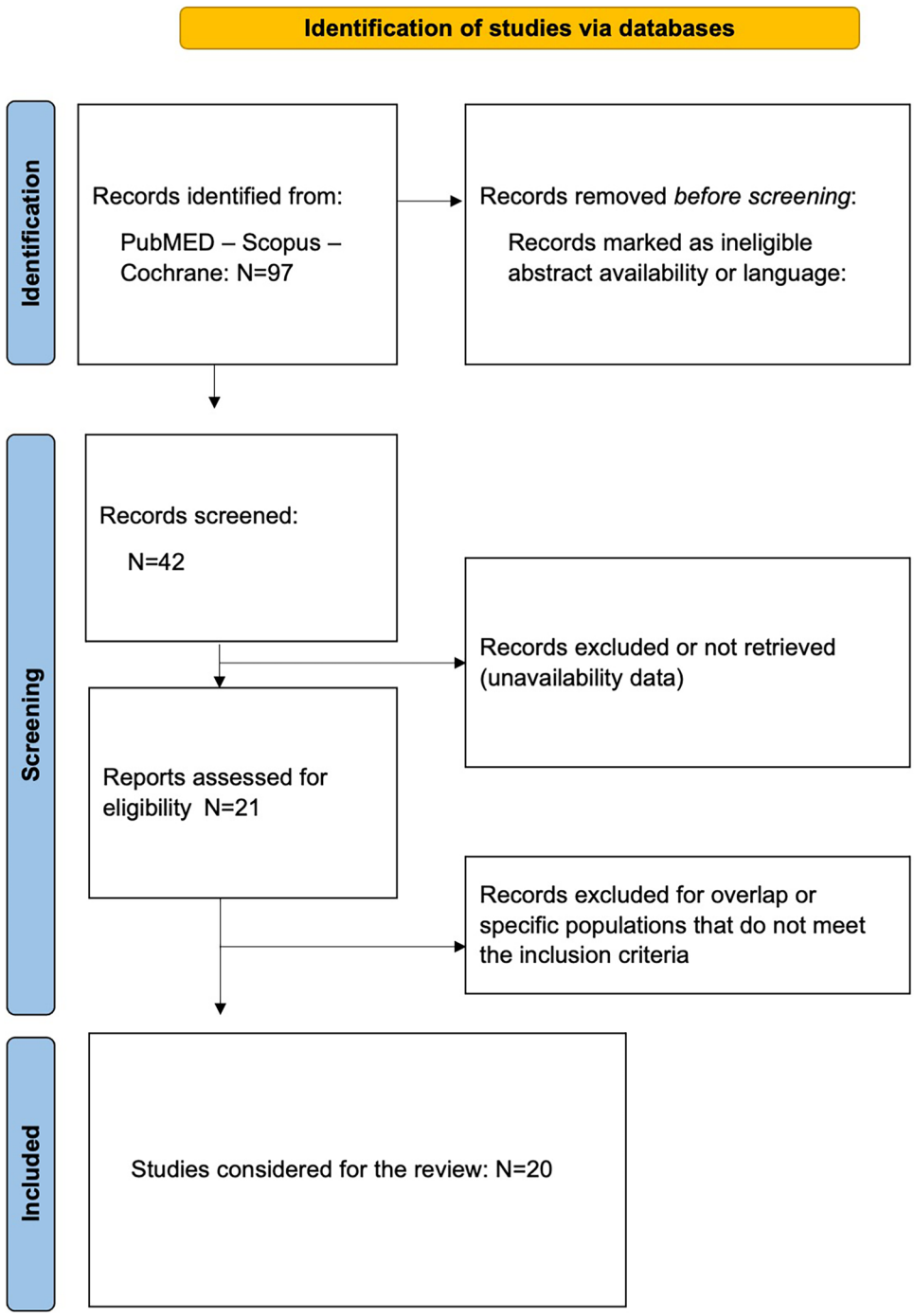

Fig. 1 Flow chart

(Table 3). Al Kholy et al. only used a breath test, which was not associated with the detection of HP in nasal tissue [30]. The follow-up period was only evaluated in one study, where authors evaluated the effectiveness of treatment on nasal outcomes [27]. The study size calculation was not evaluated in studies. Ten studies considered patients with concha bullosa, nasal fracture, or no nasal disorders for the control group (Appendix 1; Tables) [15–17, 19, 21, 22, 24–26, 31]. The control group was judged as potentially biased in studies considering patients with nasal obstruction/inferior turbinate hypertrophy as healthy individuals regarding the potential role of LPRD in the development of inferior turbinate hypertrophy. Five studies failed to demonstrate baseline group equivalence [20, 22, 24–26], which was related to differences between groups for gender ratio, comorbidities, or addiction. Statistics were commonly adequate, although a lack of study size calculation in all studies.

Table 1 Demographics and Clinical Features of Studies

References	Design	EL	N	F/M	Age	Reflux Criteria	CRS Criteria	HP Detection	HP sinonasal Outcomes
Özdek, 2003 [15]	Pros. Contr	IIB	12 CRSSNP	5/7	36	GERD	Symptoms & CT	PCR (nasal)	CRS: 4/12
			13 HC	8/5	36	symptoms			HC: 0/13
Koc, 2004 [16]	Pros. Contr	IIB	30 CRSwNP	13/17	42	GERD	Symptoms, CT	ELISA (blood)	CRS/HC: 26/30–17/20
			20 HC	9/11	40	symptoms	Histology	IHC (nasal)	CRS/HC: 6/30–0/20
Dinis, 2006 [17]	Pros. Contr	IIB	15 rCRSSNP	4/11	50	Nasal pepsin &	Recalcitrant	ureA PCR (nasal)	CRS/HC: 6/15–1/5
			5 HC	4/1	38	pepsinogen	symptoms & CT	Pepsin	CRS = HC
Kim, 2007 [18]	Pros. Contr	IIB	48 rCRS	17/31	42	NP	Symptoms & CT	CLO IHC (nasal)	CRS: 12/48
			29 HC	17/12	38				HC: 1/29
Özcan, 2008 [19]	Pros. Contr	IIB	25 CRSwNP	9/16	37	NP	Symptoms, CT,	IHC (nasal)	CRS/HC: 0/25–0/14
			14 HC	4/10	31		Endoscopy	CLO	CRS/HS: 1/25–2/14
								ELISA (blood)	CRS/HC: 7/25–3/14
Cvorovic, 2008 [29]	Pros. Contr	IIB	23 CRSwNP	11/12	43.0	GERD	Symptoms, CT,	Gastric Giemsa HP	CRS/HC: 10/23–0/15
			15 HC	7/8	37.0	Symptoms	Endoscopy	CLO (nasal)	CRS/HC: 6/23–0/15
								GERD	CRS/HC: 8/23–1/15
Ozyurt, 2009 [20]	Pros. Contr	IIB	33 CRSwNP	5/28	34	NP	Symptoms, CT,	PCR (nasal)	CRS: 19/32
			29 HC	0/27	22		Endoscopy	ureC/cagA	HC: 19/27
Burduk, 2011 [21]	Pros. Contr	IIB	20 CRSwNP	7/13	48.7	Symptoms	Symptoms, CT,	nasal ureA &	CRS/HC: 20/20–10/10
			10 HC	4/6	43.3	Signs of	Endoscopy	cagA PCRs	CRS/HC: 0/20–0/10
			30 Larynx	18/12	49.0	benign diseases		Larynx PCR	Larynx: 30–7/30
Nemati, 2011 [22]	Pros. Contr	IIB	25 CRSwNP	9/15	32.1	NP	Symptoms & CT	ureC CLO	CRS/HC: 0/25–0/25
			25 HC	15/9	24.4		Endoscopy	PCR (nasal)	
Jelavic, 2012 [23]	Pros. Contr	IIB	28 CRSwNP HP +	7/21	52	NP	Symptoms & CT	IHC (nasal)	Postop improvement:
			12 CRSwNP HP-	5/7	43		Endoscopy		HP + > HP-
Včeva, 2012 [24]	Pros. Contr	IIB	35 CRSwNP	10/25	54.0	NP	Symptoms & CT	PCR (nasal)	CRS/HC: 10/35–0/30
			30 HC	18/12	42.5		Endoscopy	ELISA	CRS/HC: 30/35–16/30
Alkholy, 2012 [30]	Pros. Uncontr	IV	40 CRSwNP	NP	29.5	NP	NP	Breath test	CRSwNP: 5/40
			104 CRSSNP						CRSSNP: 9/104
Kadhemi, 2012 [33]	Pros. Contr	IIB	37 CRSwNP	NP	NP	NP	Symptoms, CT,	PCR (nasal)	CRS-HC: 27/37–12/38
			38 HC				Endoscopy	Urease	CRS-HC: 9/37–0/38
Nikakhlagh, 2014 [25]	Pros. Contr	IIB	50 rCRSwNP	5/45	40.0	NP	Symptoms & CT	PCR (nasal)	CRS: 9/50

Table 1 (continued)

References	Design	EL	N	F/M	Age	Reflux Criteria	CRS Criteria	HP Detection	HP sinonasal Outcomes
			50 HC	24/25	30.0				HC: 2/50
Bansal, 2016 [26]	Pros. Contr	IIB	35 CRSwNP	15/20	32.0	GERD	Symptoms & CT	IHC (nasal)	CRS: 14/35
			35 HC	3/32	28.2	symptoms			HC: 3/35
Shokrollahi, 2016 [31]	Pros. Contr	IIB	51 CRSwNP*	NP	37.5	NP	Symptoms, CT,	PCR (nasal)	CRS/HC:20/62–1/25
			25 HC		31.0		Endoscopy	ELISA (blood)	CRS/HC: 9/62–1/25
Siupsinskiene, 2018 [32]	Pros. Contr	IIB	45 rCRSwNP	19/29	51.8	NP	Symptoms, CT,	PCR (nasal)	CRS/HC: 13/45–1/30
			30 HC	6/24	41.6		Endoscopy		
Lechien, 2021 [27]	Pros. Uncontr	IV	37 CRSSNP	20/17	43.5	GERD	EPOS	Gastric HP	CRS: 9/37
						symptoms		PCR culture	
Zika, 2023 [28]	Pros. Uncontr	IV	36 rCRSwNP	11/25	61.0	GERD	Symptoms & CT	Gastric HP	CRS: 28/36
						Symptoms		PCR (nasal)	CRS: 9/36
								CLO (nasal)	CRS: 11/36
								GERD	36/36

CLO Campylobacter-Like Organism; *CT* computed tomography; *CRSSNP* chronic rhinosinusitis without nasal polyps; (r) *CRSwNP* (recalcitrant) chronic rhinosinusitis with nasal polyps; *ELISA* enzyme-linked immunosorbent assay; *GERD* gastroesophageal reflux disease; *HC* healthy control; *HP* Helicobacter Pylori; *IHC* immunochemistry; *NP* not provided; *PCR* polymerase reaction chain

Table 2 Methods for Dectecting HP

HP diagnostic tools	N	References
Sinonasal PCR	11	15,17,20,21,22,24,25,28,31–33
Nasal urease test (CLO)	7	18,19,22,26,28,29,33
Sinonasal IHC	5	16,18,19,23,26
ELISA	4	16,19,24,31
Gastric Giemsa (PCR)	3	27–29
stool antigen test	1	26
Breath test	1	30

ELISA enzyme-linked immunosorbent assay; *HP* Helicobacter Pylori; *IHC* immunochemistery; *PCR* polymerase reaction chain

Discussion

Since the first study detecting HP in CRSwNP in 2003 [15], the number of studies investigating the potential association between reflux, HP, and CRS has steadily increased. To date, three hypotheses have been proposed in the literature [34, 35]. The first hypothesis suggests that the nasal cavity can be a passive reservoir of HP without association with gastric content and the development of CRS. The second hypothesis proposed that HP may originate from the oral cavity and reach the sinonasal region through oronasal reflux processes. The third hypothesis suggests that the stomach remains the primary reservoir of HP, and the HP can reach the sinonasal region through the backflow of gastric content into the upper aerodigestive tract (GERD and LPRD).

The findings of this systematic review of the literature support a substantially higher prevalence of nasal HP in patients with CRSwNP and CRSsNP (32.7–37.1%) compared to controls (3.6–14.8%). According to studies, the prevalence of nasal HP is comparable between CRSwNP and CRSsNP, which can suggest that HP is not necessarily associated with the development of polyps. Interestingly, two teams reported a strong and positive association between the severity of GERD symptoms and the presence of HP in CRS [15, 29]. These observations were, however, mitigated by Dinis et al. [17] who observed a higher rate of nasal HP in CRSwNP (40%) compared to controls (20%) but no significant differences for the nasal measurements of pepsin and pepsinogen. The observations of Dinis et al. [17] can appear as controversial regarding the other studies [15, 29], but numerous factors can limit the drawing of valid conclusions. On the one hand, this study included a low number of patients (n = 15) and controls (n = 5), which was highlighted in the MINORS assessment (13/20). On the other hand, the authors did not investigate GERD findings and partly focused on LPRD with the measurement of pepsin and pepsinogen. The consideration of pepsin and pepsinogen for the LPRD diagnosis can be biased because many patients

Table 3 MINORS

References	Clearly stated Aim	Consecutive patients	Prospective data collection	Endpoints appropriate to study	Unbiased endpoint assessment	Follow-up adequate period	<5% lost of follow-up	Study size population calculation	Adequate Control Group	Contemporary groups	Baseline Group Equivalence	Adequate Stat Analyses	Total MINORS score
Özdek, 2003 [15]	2	0	2	1	1	–	–	0	2	2	1	1	12
Koc, 2004 [16]	2	0	2	2	2	–	–	0	2	2	1	2	15
Dinis, 2006 [17]	2	0	2	2	1	–	–	0	2	2	1	1	13
Kim, 2007 [18]	2	0	2	1	2	–	–	0	1	2	2	2	14
Özcan, 2008 [19]	2	0	2	2	2	–	–	0	2	2	1	1	14
Cvorovic, 2008 [29]	2	0	2	2	2	–	–	0	1	2	1	1	13
Ozyurt, 2009 [20]	2	0	2	1	2	–	–	0	1	2	0	2	12
Burduk, 2011 [21]	2	0	2	1	2	–	–	0	2	2	1	1	13
Nemati, 2011 [22]	2	0	2	2	2	–	–	0	2	2	0	2	14
Jelavic, 2012 [23]	2	0	2	1	2	–	–	0	–	–	–	2	9
Včeva, 2012 [24]	2	0	2	2	2	–	–	0	2	2	0	2	14
Alkholy, 2012 [30]	2	0	2	0	0	–	–	0	–	–	–	2	6
Kadhemi, 2012 [33]	2	0	2	2	0	–	–	0	1	2	1	2	12
Nikakhlagh, 2014 [25]	2	0	2	1	2	–	–	0	2	2	0	2	13
Bansal, 2016 [26]	2	0	2	1	1	–	–	0	2	2	0	2	12
Shokrollahi, 2016 [31]	2	0	2	2	2	–	–	0	2	2	1	2	15
Siupsinskiene, 2018 [32]	2	0	2	1	1	–	–	0	1	2	1	2	12
Lechien, 2021 [27]	2	0	2	1	2	2	–	0	–	–	–	2	11
Zika, 2023 [28]	2	0	2	2	1	–	–	0	–	–	–	1	8

MINORS Methodological Index for Non-Randomized Studies

with a demonstrated LPRD at the 24-h HEMII-pH have no detectable pepsin in the upper aerodigestive tract [36, 37]. In that way, a recent study demonstrated that several gastroduodenal enzymes and biomarkers can be refluxed in the upper aerodigestive during the reflux events, including elastase, bile acids, trypsin, all of them having a potential role in the development of the mucosa inflammation [7, 38, 39]. Therefore, the lack of detection of pepsin or pepsinogen in nasal tissue cannot exclude the presence of a reflux disease. [13]

In most studies investigating the role of reflux in the development of upper aerodigestive tract disorders, i.e., benign lesion of the vocal cords, chronic rhinosinusitis, and otitis media, the consideration of GERD instead of LPRD was considered as the primary limitation of studies [5, 40, 41]. In the case of HP in sinonasal tissue, the consideration of GERD and less LPRD makes sense regarding their different pathophysiological mechanisms and the weight of enzymes and bacteria. Indeed, GERD is a liquid disease with backflow of the stomach into the esophagus or, in some cases of severe reflux events, into the upper aerodigestive tract [42], while LPRD primarily involves gaseous pharyngeal reflux events [43]. The weight of HP is ~ 10^{-12}g (10^{12} Da), which is significantly heavier than the molecular weight of pepsin and pepsinogen (~ 35 kDa to 50 kDa), and bile acids (~ 400–600 Da). Considering that a gaseous reflux event can transport molecules with a maximum weight of ~ 10,000–20,000 Da, it should be difficult for HP to reach the upper aerodigestive tract through a gaseous reflux event [44]. These theoretical and physiological considerations support that the detection of HP in sinonasal tissue can highlight the presence of severe GERD rather than LPRD typical reflux events (gaseous). This point strengthens the studies demonstrating the role of severe GERD in the development of CRS [45, 46]. The future studies investigating the association between reflux diseases, HP, and CRS need to consider the study of reflux events (nature, pH, duration) through the 24-h HEMII-pH, and the identification of all gastroduodenal enzymes (e.g., pepsin, trypsin, lipase, elastase, bile acids) in the sinonasal tissue of patients with CRS and HP.

The heterogeneity between studies in inclusion, exclusion criteria, and outcomes and the low number of patients and controls are the primary limitations of this review. In inclusion criteria, most studies focused on recalcitrant CRSwNP (Appendix1) but a few investigated patients with an untreated CRSwNP [19, 26], which can bias the comparison between studies. Moreover, some teams did not exclude patients with confounding factors, e.g. recent use of antibiotics, allergic rhinitis, antacids, and tobacco-alcohol consumption, that can bias the reflux/HP investigations. The consideration of patients with nasal obstruction requiring septoplasty and inferior turbinoplasty as controls is an additional limitation because reflux has been identified as a causal factor of posterior nasal turbinate hypertrophy (Mulberry turbinate) [47, 48]. Finally, the heterogeneity across studies in the method used to detect HP can influence some results outcomes, which limited the comparison between studies.

Conclusion

Helicobacter Pylori can be detected in one-third of sinonasal tissues from patients with CRS and can be considered a biomarker of GERD. The potential role of HP in the development of CRS remains unclear. The heterogeneity between studies in inclusion criteria, methods of HP detection, and reflux outcomes limit the drawing of valid conclusions.

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Declarations

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