UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Nika Puževski

Prevalence of allergic rhinitis and asthma in patients who underwent sinus surgery

GRADUATE THESIS

Zagreb, 2019.

This graduate thesis was made at Sisters of Charity University Hospital in Zagreb on Department of ORL and HNS mentored by prof. dr. sc. Tomislav Baudoin and was submitted for evaluation in the academic year 2018/2019.

Abbreviations

CF	Cystic fibrosis
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
KRS	Kronični rinosinuitis
KRSsNP	Kronični rinosinusitis s nazalnom polipozom
KRSbNP	Kronični rhinosinusitis bez nazalne polipoze
CSF	Cerebrospinal fluid
CT	Computed tomography
ENT	Ear nose throat
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ESS	Endoscopic sinus surgery
FESS	Functional endoscopic sinus surgery
GA2LEN	The Global Allergy and Asthma network of excellence
NP	Nasal polyps
NSAID	Nonsteroidal anti-inflammatory drug
HNS	Head and neck surgery
OR	Odds ratio
ORL	Otorhinolaryngology
VAS	Visual analogue scale

Table of Contents

SUMMARY

Title: Prevalence of allergic rhinitis and asthma in patients who underwent sinus surgery

Author: Nika Puževski

OBJECTIVES:

The aim of this study was to assess the prevalence of allergies or asthma in CRS patients who underwent ESS within treatment for sinonasal disease at the Department of ORL and HNS, Sisters of Charity University Hospital in Zagreb and compare the results to other studies

METHODS:

One hundred patients from ages 10 to 75 who underwent endoscopic sinus surgery in 2018, due to CRS were retrospectively reviewed. We analyzed demographics, CRS phenotypes, comorbidity of asthma and allergy and septal deformation together with different surgical procedures were collected from medical records

RESULTS:

From 100 patients that were included in our study 54% of the participants (42 males and 12 females) are diagnosed with CRSwNP and 46% (23 males and 23 females) with CRSsNP. Patients having CRSwNP show slightly higher rates of allergies of any type and asthma, however they have lower incidence of septal deformation. Furthermore, male predominance is shown both in total studied group (65%) as well as in group with allergies (70.73%) while FESS with polipectomy is shown to be the most common type of surgical procedure

CONCLUSION:

We can conclude that comorbidity of asthma and allergy has higher prevalence in patients with CRSwNP, while septal deformation in patients with CRSsNP

.

KEYWORDS: chronic rhinosinusitis; allergy; asthma; endoscopic sinus surgery (ESS)

SAŽETAK

Naslov: Učestalost alergijskog rinitisa i astme kod pacijenata nakon operacije sinusa

Autor: Nika Puževski

CILJEVI:

Cilj ovog istraživanja bio je procijeniti učestalost alergija ili astme kod bolesnika s kroničnim rinosinusitisom (KRS), koji su podvrgnuti endoskopskoj operaciji sinusa kao dio liječenja sinonazalne bolesti na Klinici za otorinolarigologiju i kirurgiju glave i vrata, KBC Sestre milosrdnice, i usporediti rezultate s drugim studijama.

METODE:

Retrospektivno su pregledane povijesti bolesti od sto pacijenata u dobi od 10 do 75 godina koji su tijekom 2018. godine bili podvrgnuti endoskopskoj operaciji sinusa. Analizirali smo emografske karakteristike,fenotipove bolesti, prevalenciju astme i alergijskih bolesti u ispitanika te vrste kirurških zahvata.

REZULTATI:

Od 100 bolesnika koji su bili uključeni u naše istraživanje, 54% ispitanika (42 muškarca i 12 žena) dijagnosticiran je kronični rinosinuitis s nazalnom polipozom (KRSsNP), dok je 46% ispitanika (23 muškarca i 23 žene) dijagnosticiran kronični rinosinuitis bez nazalne polipoze (KRSbNP). Bolesnici koji imaju KRSsNP pokazuju nešto veću sklonost alergijama bilo koje vrste i astmi, ali imaju manju učestalost septalne deformacije.. Više je bilo muškaraca ukupno(65%) kao i u skupini ispitanika s alergijama(70.73%) , a FESS s polipektomijom je najčešće izvođen zahvat (42%)

ZAKLJUČAK:

Možemo zaključiti da je komorbiditet astme i alergije učestaliji u bolesnika s KRSsNP,a septalna deformacija u bolesnika s KRSbNP.

KLJUČNE RIJEČI: kronični rinosinuitis; alergija; astma; endoskopska sinusna kirurgija

1. Introduction

Rhinosinusitis, in its various forms, constitutes, one of the commonest conditions encountered in medicine and may present to a wide range of clinicians, including primary care, pulmonologists, allergists, otorhinolaryngologists, neurosurgeons and more, especially when complications occur. It is an inflammation of the mucosa of the nose and paranasal sinuses characterized by two or more symptoms [1,2,3,4]; one of each should be either nasal discharge (anterior or posterior nasal drip), obstruction, blockage, congestion with or without facial pain or pressure and/or with or without smell disturbances. In addition, endoscopic signs of rhinosinusitis are nasal polyps, that can be followed with or without mucopurulent discharge and/or edema/mucosal obstruction, both originating primarily in the middle meatus [1,2]. Finally, mucosal changes within the osteomeatal complex or sinuses can be demonstrated on the CT scan. We need to address that the disease is divided into acute (i.e. <12 weeks with complete resolution of symptoms) and chronic (i.e. >12 weeks without complete resolution of symptom) with possible etiologies being either viral or bacterial. Viral rhinosinusitis, which is a more common type, should be diagnosed when symptoms or signs of acute rhinosinusitis are present for <10 days and the symptoms are not worsening. In contrary, bacterial rhinosinusitis is presumed when symptoms or signs of acute rhinosinusitis fail to improve within 10 days beyond the onset of upper respiratory symptoms, or the symptoms worsen within 10 days after an initial improvement (double worsening). This paper will mostly concentrate on chronic rhinosinusitis (CRS) and explain its various types and subtypes, diagnosis and clinical severities. In addition to these, its correlation to asthma and allergies will be mentioned together with treatment modalities, in particular addressing endoscopic sinus surgery.

2. Chronic rhinosinusitis

Pathogenesis of CRS

Few hypotheses have been proposed in order to explain the pathophysiology of CRS; the first attempt to address it was the "fungal hypothesis", which attributed all CRS to an excessive host response to Alternaria fungi [5,6]. This was rejected by many investigators as originally proposed; however, fungi are still believed to play a role in at least some forms of CRS. Defects in eicosanoid pathway have also been proposed as a potential cause of CRSwNP [7,8]; specifically, increased synthesis of pro-inflammatory leukotrienes and decreased synthesis of anti-inflammatory prostaglandins (PGE2). This theory is controversial due to lack of clinical efficacy with leukotriene pathway inhibitors. The microbiology of CRS differs from that of acute rhinosinusitis. In addition to standard pathogens; *Streptococcus pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis*, there is an increased prevalence of *S. aureus*, *Pseudomonas aeruginosa* and anaerobic bacteria in CRS. The "staphylococcal superantigen hypothesis" suggested that exotoxins have a key role in nasal polyposis via effects on multiple cell types [9,10]. The net effect is Th2 skewing, Treg inhibition, increased eosinophils and mast cell activity, and increased tissue damage and remodeling. Furthermore the "immune barrier hypothesis" suggests that dysfunction in the mechanical barrier and/or innate immune response of the sinonasal epithelium manifests as CRS. This, theoretically, leads to colonization of the mucosa with increased multiple microbial agents, heightened barrier damage, and a compensatory adaptive immune response [11,12]. Lastly, biofilm formation is said to be facilitated by a defect in the innate immune barrier, the mechanism in CRS is unclear, but biofilms on the sinus mucosa have been linked to those mediating periodontal disease [13,14]. Thus, host susceptibility to complex diseases such as CRS involves multiple genetic factors but also environmentally-determined epigenetic changes. Ongoing environmental stresses confront the susceptible host, which may lead to the development of the chronically inflamed state of CRS.

Epidemiology of chronic rhinosinusitis

CRSsNP- due to the heterogeneity of the disorder and the diagnostic imprecision often made by clinicians, accurate prevalence of CRS remains speculative. In surveys of chronic conditions, CRS was found to affect 15.5% of the total adult population in one survey [15] and 16% in the

second, defined as having 'sinus trouble' for more than 3 months in the years before the interview [16]. However, the prevalence of doctor-diagnosed CRS is much lower, a prevalence of 2% [17]. The majority of primary care physician do not have the equipment necessary to properly diagnose CRS, which leads to overdiagnosis. The prevalence rate is higher in female with a female/male ratio of 6/4 [16]. In a postal questionnaire sent to a random sample of adults aged 15-75 years in 19 centers in Europe, The Global Allergy and Asthma Network of Excellence (GA2LEN) concluded that the overall prevalence of CRS by EP3OS criteria was 10.9% (range 6.9-27.1) [18].

CRSwNP- studies rely on nasal endoscopy and/or questionnaires to report on the prevalence of nasal polyps. Large nasal polyps can be visualized by anterior rhinoscopy, whereas nasal endoscopy is needed for smaller nasal polyps. Recently, a panel of French experts specializing in ENT elaborated a questionnaire/algorithm with 90% sensitivity and specificity [19]. For the epidemiologic research, a distinction between asymptomatic nasal polyps and symptomatic nasal polyps needs to be made. Asymptomatic polyps may transiently be present and hence remain undiagnosed. Symptomatic polyps may remain undiagnosed, either because they are missed during anterior rhinoscopy or because patients do not seek medical attention for this problem. In comparison, patients who are actively seeking medical care for CRSwNP had more extensive nasal polyps with greater reduction in peak inspiratory flow and more impairment of the sense of smell. We need to say that nasal polyps occur in all races and become more common with age (uncommon under the age of 20) and their onset has a close linear association between the mean age of onset with rhinitis, asthma and NSAID intolerance.

Factors associated with CRSsNP and CRSwNP

Even though most important factors will be mentioned, allergy and asthma are excluded in this list since they will be mentioned in separate paragraphs.

- **Ciliary impairment**- the ciliary in the body is responsible for the clearance of the sinuses and prevention of prolonged inflammation. CRS with long history of respiratory infections is common, as expected, in patients with primary disorders involving the ciliary function, including Kartagener's syndrome and primary ciliary dyskinesia. In Cystic fibrosis (CF), the viscous mucous that is produced causes malfunction of the cilia

and consequently CRS. Nasal polyps (primarily neutrophilic) are present in about 40% of patients with CF [20].

- **Nasal septal deformation**- nasal septal deviation is a common disorder that presents in up to 62% of the population, and its role in the pathogenesis of chronic sinusitis remains uncertain. Nasal septal deviation may either cause osteomeatal obstruction or may interfere with proper airflow and results in sinusitis.
- **Aspirin sensitivity**- in patients with aspirin sensitivity 36-96% have CRSwNP [21-27] and up to 96% have radiographic changes affecting their paranasal sinuses [28].
- **Immunocompromised state**- development of dysfunctional immunity may occur later in life and present with CRS. Congenital immunodeficiencies manifest themselves with symptoms early in life. An unexpectedly high incidence of immune dysfunction was found in a retrospective review of patients with refractory sinusitis [29]. Low Immunoglobulin levels, IgA and IgM titers were found in 18%, 17%, and 5%, respectively. Common variable immunodeficiency was diagnosed in 10% and selective IgA deficiency in 6% of patients. Thus, immunological testing should be an integral part of the diagnostic pathway of patients with CRS.
- **Genetic factors**- genetic factors have been shown to have a role such as patients with cystic fibrosis and primary ciliary dyskinesia [30] and there is some evidence for CRSwNP. Although CRSsNP have been observed in family members, no genetic abnormalities have been linked to CRSsNP.
- **Pregnancy and endocrine state**- nasal congestion occurs in approximately one-fifth of pregnant women [31]. The pathogenesis is unclear but several theories have been proposed: direct hormonal effect of estrogen, progesterone, and placental growth hormone on the nasal mucosa, and indirect effects such as vascular changes, may be involved. In addition, thyroid dysfunction has been implicated in CRS, but the data is limited.
- **Local host factors**- several anatomic variations have been suggested to contribute to the development of CRS such as nasal septal deviation, concha bullosa, and uncinate process displacement [32]. However, studies have failed to reveal any significant correlation between anatomical variation and increased prevalence of CRSs or wNP than in a control group [33-35]. In spite of the observation that sinonasal complaints often resolve after nasal

surgery, this does not imply that anatomical variation is etiologically involved. Taken all together, so far, there is no supportive evidence for a casual association between nasal anatomic variations and incidence of CRS.

- **Biofilms**- the surface of nasal polyps is colonized by many biofilm-forming pathogenic bacteria that may not be the primary etiologic agent in NP, but a contributor significantly adding more inflammation.
- **Environmental factors**- several studies have demonstrated the association of smoking with CRS, including exposure to secondhand smoke [(36)]. Studies have investigated the relationship between CRS and occupational exposure and have concluded that there was an increased prevalence ratio in plant and machinery operators and assemblers, elementary occupations, craft workers and the unemployed

Classification of chronic rhinosinusitis

For research purposes, chronic rhinosinusitis is defined as per the clinical definition mentioned above. For the purpose of this study, CRS is further divided endoscopically into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP):

- Chronic rhinosinusitis with nasal polyps: bilateral, endoscopically visualized in the middle meatus
- Chronic rhinosinusitis without nasal polyps: no visible polyps in the middle meatus

In order to avoid overlap, this definition accepts the idea that there is a spectrum of disease in CRS, which includes polypoid changes in the sinus and/or middle meatus but, excludes those with polypoid disease presenting in the nasal cavity. However, to avoid overlap, once the surgery has altered the anatomy of the lateral wall, the presence of polyps is defined as bilateral pedunculated lesions as opposed to cobblestoned mucosa > 6 months after surgery on endoscopic examination.

Diagnosis, Symptomatology and Complications of CRS

Assessment of rhinosinusitis is based on symptoms:

- Nasal blockage, congestion, or stuffiness;
- Nasal discharge or postnasal drip, often mucopurulent;
- Facial pain or pressure, headache, and
- Reduction or loss of smell.

In addition, distant and general symptoms occur; distant symptoms are pharyngeal, laryngeal and tracheal irritation causing sore throat, dysphonia and cough, whereas general symptoms include malaise, drowsiness and fever. The symptoms are principally the same in acute and chronic rhinosinusitis with and without polyps, but the symptom pattern and intensity may vary. Acute forms of infections have usually more distinct and severe symptoms.

Diagnosis of CRS

Chronic rhinosinusitis, with or without nasal polyps in adults is defined as:

- Inflammation of the nose and paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) for >12 weeks
- +/- facial pain or pressure
- +/- reduction or loss of smell

This should be supported by demonstrable disease. Either endoscopic signs of:

- Nasal polyps, and/or
- Mucopurulent discharge primarily from middle meatus, and/or
- Edema/mucosal obstruction primarily in middle meatus

And/or CT changes:

- Mucosal changes within ostiomeatal complex and/or sinuses.

It is appropriate that the definition is symptoms based, as it is this that drives patients to seek medical care for their CRS. However, the presence of supporting findings is important to exclude

differential diagnoses. For the majority of patients, diagnosis is made in primary care based on symptoms alone.

Symptoms reported in CRS

In addition to the symptoms listed above, there are several minor symptoms including ear pain or pressure, dizziness, halitosis, dental pain, distant and general symptoms including nasal, pharyngeal, laryngeal and tracheal irritation, dysphonia and chough, drowsiness, malaise and sleep disturbances, presenting in numerous combinations [37,38].

Nasal obstruction is one of the most common symptoms reported with CRS. Its components include: congestion due to dilation of venous sinusoids as a result of inflammation and edema, nasal fibrosis and nasal polyposis. Nasal discharge, either anterior or posterior, may vary greatly in composition. Patients may report profuse watery discharge or thick purulent discharge. Facial pain is one of the most variable symptoms, with reported prevalence in patients with CRS ranging from 18%-77.9% [39,40]. In addition, diagnosis of CRS is associated with a 9-fold increased risk of reporting chronic headache compared with the general population, and symptoms were significantly improved with surgery and nasal corticosteroids treatment [41]. Olfactory disturbance is common too, due to edema in the area and physical prevention odorants reaching the olfactory cleft. In a study of 367 patients with a diagnosis of CRS, the presence of polyps was associated with increased risk of hyposmia (OR 2.4 95% CI 1.3-4.2, P=0.003) and anosmia (OR 13.2, 95% CI 5.7-30.7, P<0.001) compared with non-polyp CRS [42]. Sleep impairment is another common disturbance associated with CRSwNP and CRSsNP patients. The key cause is thought to be sleep-disordered breathing that is associated with nasal congestion. This can lead to fatigue, daytime somnolence, impaired daytime functioning as reflected in lower level of productivity at work or school, and a reduced quality of life [43-45]. There is a growing amount of evidence that reduction in congestion with nasal corticosteroids is associated with improved sleep, reduced daytime sleepiness, and enhanced quality of life [46].

Assessment of symptom severity

Different grading tools can be used to estimate the severity of the overall symptoms of CRS;

- Recorded as severity: no symptom, mild, moderate or severe
- Recorded as numbers: from 0 to 5 degrees or more
- Recorded as VAS score on a line giving measurable continuum (1-10).

Strength, degree and duration should be assessed in each patient. The duration of symptoms is evaluated as symptomatic or symptom-free periods (expressed as hours per day or as days per week). According to VAS score, a validation study has shown 'mild disease' to be defined as a VAS score of 0-3, moderate >3-7, and severe as >7. In general, quality of life is affected with scores of 5 or more.

Complications of Chronic rhinosinusitis

Complication of chronic rhinosinusitis, with or without polyps, are rare and largely due to its effects on the surrounding bone. They generally result from an imbalance in the normal process of bone resorption, regeneration and remodeling, and are far less common than those associated with acute infection and inflammation. In some cases, they may be considered as a manifestation of the natural history of the disease. The complications may include:

- Mucocele formation
- Osteitis
- Bone erosion and expansion
- Metaplastic bone formation
- Optic neuropathy

However there is no evidence the CRS is associated with neoplastic changes, either benign or malignant.

Treatment modalities in CRS

The goal of the treatment in CRS is to reduce mucosal inflammation, to control infections, and to restore mucociliary clearance within the sinuses. Eosinophilic inflammation is one of the hallmarks of CRS [47], and reducing mucosal eosinophilia is one of the therapeutic goals. In the management of CRS there is no such thing as mono-regimen, and treatment should be individualized. For those patients with whom allergy, pollution, or mold exposures appear to be a risk factor, environmental control is an important modality. Sinus surgery is generally reserved for patients who remain symptomatic despite maximal medical therapy. In this section, different treatment modalities will be presented, with further focus on endoscopic sinus surgery.

Corticosteroids

Topical corticosteroids constitute the first-line therapy in the management of CRS. Long term treatment with intranasal steroids has been shown to reduce sinus inflammation and nasal polyp size and improve associated symptoms [48-50]. Oral steroids are used in the treatment of CRS with nasal polyps and in the cases of severe CRS when rapid symptomatic improvement is needed [51,52]. Topical and systemic steroids reduce eosinophil chemotaxis and increase their apoptosis, they also decrease white blood cell migration, production of inflammatory mediators, antibody production, histamine release, and swelling [53].

- **Topical nasal steroids**- several studies have demonstrated that topical steroids are beneficial in the treatment of CRS, especially when small to medium-sized polyps are involved and for rhinitis symptoms [53, 54]. In addition, corticosteroids have been shown to delay recurrence of polyps after surgery [55]. Common side effects with intranasal steroid use include nasal irritation, mucosal bleeding, and crusting [50,52].
- **Systemic steroids**- oral steroids have been effective in treating allergic rhinitis, providing rapid relief of facial pain or pressure, nasal blockage by reducing mucosal edema, especially in patients with CRSwNP [56,57]. In a study of 25 patients with CRSwNP with massive polyps, treatment with high-dose oral prednisolone was associated with both subjective and objective improvement and involution of nasal polyps [58].

The daily usage of topical nasal steroids appears to be associated with minimal risks, however, long-term systemic steroids is associated with significant side effects [50,52]. Therefore, a tapered

regimen of oral steroid is given during severe flare-ups of CRS or in the postoperative period after sinus surgery.

Nasal irrigation

Saline nasal irrigation has been advocated as an adjunct therapy for CRS. The procedure promotes mucociliary clearance by flushing out mucus, crusts, and irritants. In addition, cavity irrigation brings enhancement of ciliary activity, removal of antigen, biofilm, or inflammatory mediators, and a protective role on the sinonasal mucosa [(59)]. Nasal irrigation is also useful after endoscopic sinus surgery to clear crusts and mucus that appear postoperatively. Hypertonic saline is often used and have been described to have a beneficial role in decongesting the nose through an osmotic mechanism [(60)]. Budesonide have been added too as an adjuvant method of treating sinus inflammation. Its use after sinus surgery decreases mucosal inflammation, shortening the stage of epithelization and accelerates the recovery of the mucosa [(61)].

Antibiotics

Most experts agree the antimicrobials for the treatment of CRS should provide broad-spectrum coverage. Commonly used antibiotics include amoxicillin-clavulanate, ciprofloxacin or levofloxacin, clindamycin, and trimethoprim/sulfamethoxazole. The bacterial flora cultured from purulence in cases of CRS tends to demonstrate increased antibiotic resistance. Antibiotics are typically used for 3-4 weeks in order to maximize the anti-inflammatory effect, to lower bacterial loads, and to treat acute exacerbations of CRS. The potential association between fungi and inflammation in CRS has generated interest in the use of antifungal agents too.

Other medical treatments

No randomized clinical trials for the treatment of CRS were found regarding antihistamines, mucolytics and expectorants, homeopathic remedies, proton pump inhibitors, and surfactants including baby shampoo or nasal decongestants. These treatment modalities are not recommended, but may provide temporary symptomatic relief.

Surgical Modalities

If medical treatments have not been successful in improving sinus symptoms, endoscopic sinus surgery may be helpful. The main goal of sinus surgery is to improve the drainage pathway of the sinuses. By widening the natural drainage pathway of the unhealthy sinuses, sinus infections should be reduced. Patients with obstruction or blockage of their sinuses due to their sinus anatomy do very well with sinus surgery. Many patients who also have a problem with inflammation of the sinus lining (mucous membrane usually improve with sinus surgery because creating the larger sinus opening will allow better sinus drainage and more rinses/medication to get into the sinuses and help treat the diseased lining. One of the most important benefits of surgery is the ability to deliver medications (sprays, rinses, nebulized drugs) to the lining of the sinuses after they have been opened. Therefore, sinus surgery is done in addition to, and is not a replacement for, proper medical treatment of the sinuses. It is important to note that the patients who have diseased mucous membranes or a form of nasal polyps, no amount of surgery can change this fact. For many patients, surgery may not be a cure for sinusitis, but it is one of the many critical steps in managing sinus disease.

Surgical interventions used for CRS primarily involve open surgery, which is aimed at mucosal stripping within the maxillary or frontal sinuses, or ethmoidectomy performed with limited visualization. Such surgery has almost completely been replaced by endoscopic sinus surgery (ESS). ESS is associated with significantly lower morbidity and higher success rates than previous surgical approaches [(62)]. ESS may be done under local or general anesthesia. Local anesthesia involves numbing the nasal/sinus cavity, but the patient remains awake (or lightly sedated). General anesthesia means that the patient goes to sleep with anesthesia for the surgery. ESS involves the use of nasal endoscope that is inserted through the nostril to view the nose and sinuses. The goal of the surgery is to identify the narrow channels that connect the sinuses to the nose, enlarge these narrow openings/channels, and improve the drainage from the sinuses into the nose. Most people have four sinuses on each side of their face, for a total of eight sinuses. These are the maxillary, ethmoid, sphenoid, and frontal sinuses. The maxillary sinuses are in the cheek, the ethmoid sinuses are between the eyes, the sphenoid sinuses are almost exactly in the center of the head, and the frontal sinuses are in the forehead. It is possible that one may not have all of these sinuses due to differences from person to person, or one's sinus may have already been opened by previous surgery. Sinusitis may affect some or all of the sinuses.

Surgery for CRSwNP

Twenty percent of CRS patients have nasal polyps. From a clinical, radiological, and histological point of view the mucosal inflammatory response is more florid in CRS patients with nasal polyps than in those without, and the relapse rate after surgery for nasal polyps is much higher [(63)]. Surgical intervention in the treatment of nasal polyps is preserved for patients who fail to improve after a trial of maximal medical therapy. Functional Endoscopic Sinus Surgery (FESS) involves the clearance of polyps and polypoid mucosa and opening of the sinus ostia. Removal of the inflammatory tissue and the reduction in load of antigens mediating this inflammation, as well as the improvement of the sinus ventilation and mucociliary clearance, are the probable mechanisms whereby FESS improves symptoms in CRSwNP. The outcome of sinus polypoid surgery is influenced by whether the polyps are idiopathic or related to an underlying mucosal condition such as aspirin-induced respiratory disease, cystic fibrosis, or primary ciliary dyskinesia. However, in both idiopathic and secondary cases, the long-term efficacy of ESS is dependent on the regimen of medical treatment prescribed postoperatively and the subsequent compliance to this regimen.

Efficacy of surgery for nasal polyps

Endoscopic sinus surgery for nasal polyposis has been generally reported to be a safe and effective procedure. A number of series have demonstrated that sinus surgery in patients with nasal polyps can result in a prolonged reduction of nasal symptoms and an improvement in quality of life. Dalziel et al. evaluated 33 articles published between 1978 and 2001 [(64)]. Seven studies included only patients with polyps and 26 had CRS with and without polyps. Patients judged their symptoms to be 'improved' or 'greatly improved' in 75 to 95% of cases. The percentage of overall complications was low (1.4% for FESS compared to 0.8% for traditional procedures). The implications of this review are that FESS is safe and effective treatment for the great majority of patients. Even though there is some evidence that a significantly higher rate of recurrent surgery is required in patients with nasal polyposis than those without polyps, patients with polyps may have more improvement following sinus surgery than CRSsNP patients [(65,66)].

Complications of sinus surgery

The list of the complications in this paragraph is not intended to be all-inclusive, but rather to highlight some of the more common complications that are worth mentioning [67];

- **Bleeding:** It is normal to have some degree of bleeding after surgery on the nasal septum or turbinates. Rarely does this require additional intervention and extremely rarely does it require blood transfusion. Non-steroidal anti-inflammatory and certain over-the-counter supplements such as vitamin E and gingko can increase the risk of bleeding, so patients should consult with their physicians regarding the use of any medications before or after surgery. Postoperative bleeding most commonly occurs within the first 24 hours of the procedure, but can be delayed days or even weeks. In case of septal hematoma removal of the hematoma is necessary, and the development of scar tissue or even nasal collapse could occur.
- **Infection:** The most common reason to undergo sinus surgery is a chronic sinus infection that does not resolve with medications. The patient with sinusitis is therefore at risk of developing certain other infections in this area (abscesses, meningitis, etc.) from sinus surgery, although it important to recognize that this is also a complication of not undergoing surgery for a refractory chronic sinus infection.
- **Impaired sense of taste or smell:** The sense of smell usually improves after the procedure because airflow is restored, although in sporadic cases it could worsen depending on the extent of swelling, infection, or allergy. This impairment is often temporary, but can be prolonged.
- **Voice changes:** One of the functions of the sinuses is to affect resonance, so vocal professionals should be aware of potential changes in their voice after sinus surgery.
- **Nasal obstruction:** Surgery typically improves airflow, but in some patients, it may not improve or rarely may worsen. Small scar bands may occur in the nose and require removal by the surgeon at postoperative visits.
- **Numbness:** Numbness of the front upper teeth, lip or nose may occur after surgery, but it is usually self-limiting and does not require further treatment.
- **Pain and dryness:** turbinates are “swell bodies” that are present along the sidewall of the nasal cavity. They often become too enlarged and their size is physically reduced during

nasal surgeries, and this often improves symptoms such as nasal congestion of obstruction. However, in some patients this may leave them with the sensation of being overly dry or even cause chronic pain; a very rare, but severe form of this is referred to as "empty nose syndrome."

- **Intraorbital complications:** The eye is situated directly next to several of the paranasal sinuses and is separated from them by a thin layer of bone. Because of the close proximity, in rare cases, bleeding may occur into the orbit, requiring treatment at the time of the initial surgery. Visual loss and blindness have been reported, but are extremely rare. Another uncommon problem is damage to the muscles that move the eye, leading to double vision, which can be temporary or permanent. In certain circumstances, there may be a change in the function of the tear ducts causing excessive tearing. Since the eye is in close proximity to the sinuses, a major orbital complication or blindness could possibly occur even without surgery for patients with severe or refractory CRS.
- **Intracranial complications:** The floor of the brain is where the septum attaches to the roof of the nose. If this thin bony layer is fractured, CSF can leak into the nose. While rare, this is likely to be identified and repaired in the operating room at the time of the primary surgery. In rare cases, this could lead to infection of the meninges, bleeding into the brain, or the need for further intracranial surgeries.

Recovery

Some nasal packing may be used during surgery, although in general, this is less common than it was in the past. The operating surgeon will determine whether nasal packing will be used. The recovery period will vary depending on the surgery performed and the individual patient. Many people do not have much pain after sinus surgery, but every patient is different. Depending on the extent of the surgery, one may be prescribed stronger pain medicine. Generally, postoperative discomfort, congestion, and drainage should improve after the first few days, with mild symptoms sometimes lingering several weeks after the surgery. Because sinus surgery is just one step in treating sinus disease, the surgeon may also place you on medications that can include saline rinses, nasal steroid sprays, and possibly antibiotics.

3. Allergy and asthma in correlation with CRS

Allergy and CRS

Review articles on CRS have suggested that atopy predisposes to its development [68,69]. It is tempting to speculate that allergic inflammation in the nose predisposes the atopic individual to the development of CRS since both conditions share the same trend of increasing prevalence [70,71] and are frequently associated. It has been postulated [72] that swelling of the nasal mucosa in allergic rhinitis at the site of the sinus ostia may compromise ventilation and even obstruct sinus ostia, leading to mucus retention and infection. A number of studies report that markers of atopy are more prevalent in populations with CRS. Benninger reported that 54% of outpatients with CRS had positive skin prick tests [73]. Among CRS patients undergoing sinus surgery, the prevalence of positive skin prick tests ranges from 50% to 84%, of which the majority (60%) has multiple sensitivities [74-76]. However, the role of allergy in CRS is questioned by other epidemiologic studies showing no increase in the incidence of infectious CRS during the pollen season in pollen-sensitized patients [77]. Taking all into account epidemiologic data show an increased prevalence of allergic rhinitis in patients with CRS, but the role of allergy in CRS remains unclear

Asthma and CRS

Bronchial asthma is considered a comorbid condition of CRS. In a recent large-scale European survey, the strong association between CRS and asthma was confirmed [78]. In some centers, around 50% of patients with CRS have clinical asthma [79,80]. Studies on radiographic abnormalities of the sinuses in asthmatic patients have shown a high prevalence of abnormal sinus mucosa [81,82]. CRSwNP and asthma are frequently associated in the same patients, though the inter-relationship is poorly understood [83]. The association of CRS with asthma was stronger in those reporting both CRS and allergic rhinitis. Wheezing and respiratory symptoms are present in 31% and 42% of patients with CRSwNP, and asthma is reported by 26% of patients with CRSwNP, compared to 6% of control group [84,85]. In addition, 7% of patients with asthma has NP [86]. NP take between 9 to 13 years to develop, but only two years in aspirin-induced asthma [86] 10% will develop both polyps and asthma simultaneously and the remainder develop first polyps and asthma later [87]. Interestingly, most patients with CRS who do not report to have

asthma show bronchial hyperresponsiveness when given a metacholine challenge test [88]. Histopathologic features of CRS and asthma largely overlap. Heterogeneous eosinophilic inflammation and features of airway remodeling like epithelial shedding and basement membrane thickening are found in the mucosa of CRS and asthma [88]. Cytokine patterns in sinus tissue of CRS highly resemble those of bronchial tissue in asthma [89], explaining the presence of eosinophils in both conditions. Finally, lavages from CRS patients show that eosinophils were the dominant cell type in both nasal and broncho-alveolar lavages in the subgroup of patients with CRS with asthma [90]. GA2LEN studied over 52,000 adults aged 18-75 years and living in 19 centers in 12 countries and concluded that there was a strong association of asthma with CRS. The association with asthma was stronger in those reporting both CRS and allergic rhinitis [91]. Even though interaction between both rhinosinusitis and asthma is not always clinically present, as Ragab et al. [90] found no correlation between rhinosinusitis and asthma severity. However, patients with asthma showed more CT scan abnormalities than non-asthmatic patients [92], and CT scan abnormalities in severe asthmatic patients correlated with sputum eosinophilia and pulmonary function [93].

4. Hypothesis

In this study, we hypothesized that a significant proportion of patients with CRS have asthma or allergy of any kind.

5. Objectives

The aim of this study is to investigate the prevalence of allergies and asthma in patients with different sinonasal diagnoses and their distribution according to demographics and type of endoscopic surgical procedures which were performed to treat sinonasal diseases, in the Department of ORL and HNS, Sisters of Charity University Hospital, during the 2018.

6. Material and Methods

This study is a randomized retrospective study done on the ENT department at Sisters of Charity University in Zagreb. Caracteristics of 100 patients who were diagnosed with CRS and who underwent ESS in 2018 were taken from the medical data. The patient medical record collected also included disease phenotype, age, sex, septal deformation, allergies and asthma. For views and statistical calculations, Microsoft Excel Office was used.

7. Results

A total of 100 patients were reviewed among which 65 were male and 35 were female. In this study the youngest patient was 10, while the oldest was 75 years old. The patients were divided into 2 main groups according to their disease phenotype (Table 1, Figure 1). 54 of patients were diagnosed with CRSwNP, while 46% were diagnosed with CRSsNP. Different variables were taken from the participants and they include demographic view, their personal history regarding allergies and asthma (Table 2, Figure 2) as well as septal deformation and type of the endoscopic sinus surgeries performed (Table 3).

Table 1 Disease phenotype among studied group of patients

	Male	Female	Overall
Number	65	35	100
CRSwNP	42	12	62
CRSsNP	23	23	46

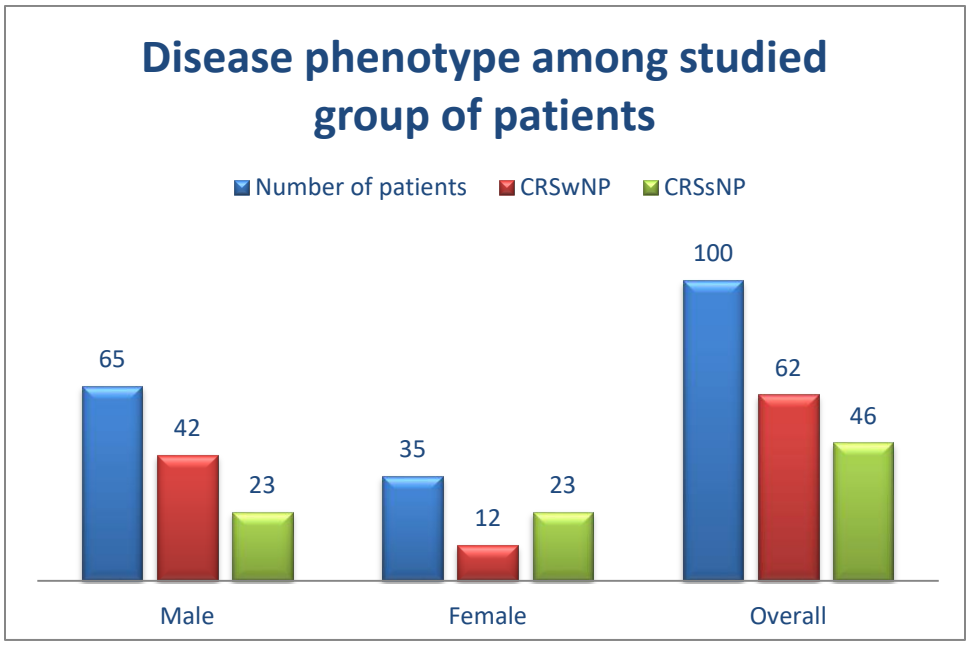

Figure 1 Prevalence of disease phenotype among studied group

Table 2 Prevalence of allergies and asthma

	Male	Female	Overall
Allergies	29	12	41
Asthma	7	8	15

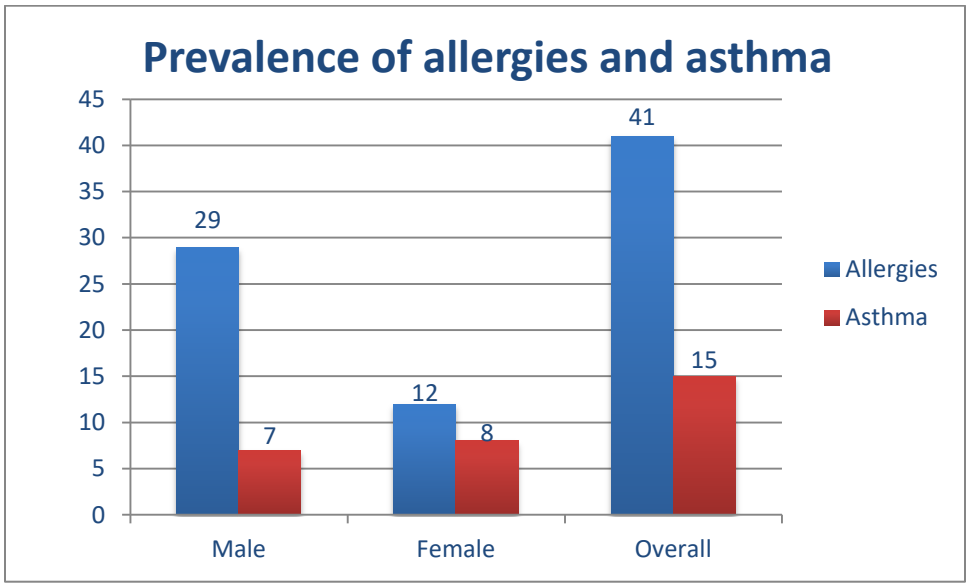

Figure 2 Prevalence of allergies and asthma between studied group

Table 3 Endoscopic sinus surgeries that the studied group has been subjected to

	Male	Female	Overall
FESS	5	12	17
FESS + SEPTOPLASTY	12	5	17
FESS + SEPTOPLASTY + POLYPECTOMY	10	1	11
FESS + SEPTOPLASTY + RF MUCOTOMY	3	4	7
FESS + RF MUCOTOMY	6	2	8
FESS + POLYPECTOMY	30	12	42

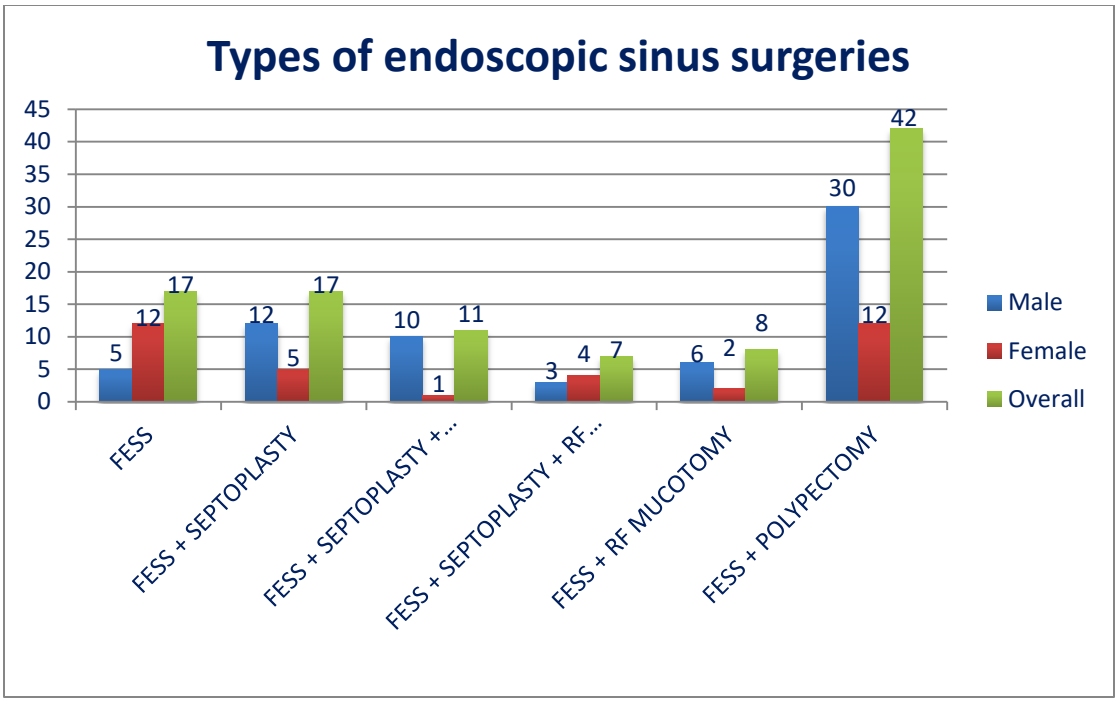

Figure 3 Types of different endoscopic sinus surgeries

During the research we were trying to establish if the majority of patients having allergies, asthma or aspirin sensitivity also have CRSwNP or CRSsNP. Figure 4 shows higher incidence of all aforementioned comorbidities in the patients having CRSwNP.

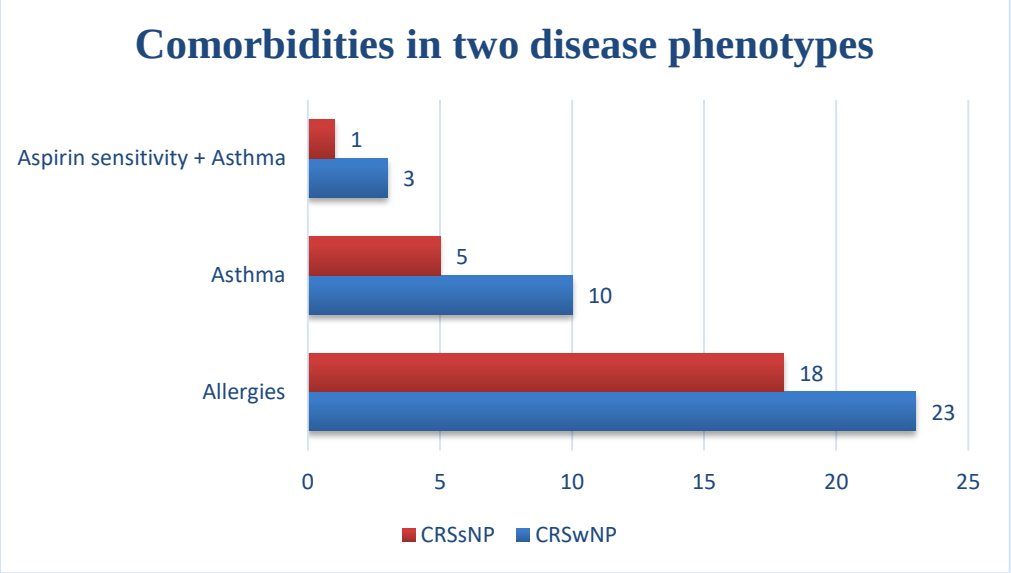

Figure 4 Incidence of comorbidities in patients having CRSwNP and CRSsNP

We have also observed prevalence of different allergy types among male and female patients and results are shown in Figure 5.

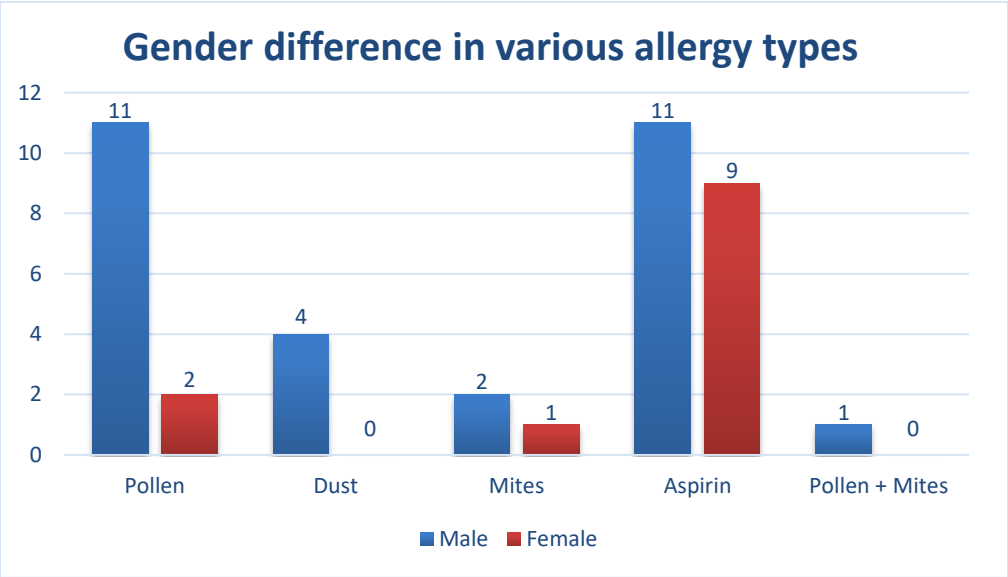

Figure 5 Prevalence of different allergy types among studied group

8. Discussion

Sinusitis is one of the most common diseases of the nose and paranasal sinuses. Recent data have demonstrated that CRS affects approximately 5–15% of the general population [(94-98)]. Nasal polyposis, considered as a subgroup of CRS represents a big group of patients with an incidence of 4% in general population [(99)] and 25–30% in patients suffering from CRS [(100)]. Although both are characterized by mucopurulent drainage and nasal obstruction, CRSsNP is frequently associated with facial pain/pressure/fullness whereas CRSwNP is frequently characterized by hyposmia. Nasal polyps (CRSwNP) are defined as pedunculated lesions as opposed to cobblestoned mucosa, endoscopically visualized in middle meatus [(101)] which reportedly occur in 0.5% to 4.3% of the population [(102)]. The prevalence tends to increase with age and the disease occurs more often in men. In our study, in the CRSsNP group, out of the participants who underwent ESS there were 23 males and 23 females while in the CRSwNP there were 42 males and 12 females which shows male predominance mentioned earlier. Furthermore, to show that the prevalence of patients who underwent ESS have CRSwNP the UK National Sinonasal audit

did a multi-center prospective cohort study, largest of its kind [66], from 87 hospitals and 298 UK Consultant Otorhinolaryngologists, in which 70 % of the 3128 patients had nasal polyps, and 30 % did not. In contrary, our study did not show such a big difference by having 54% patients from the studied group with CRSwNP and 46% with CRSsNP. Besides two different disease phenotypes, we were also focused on additional comorbidities. We need to mention that any anatomical, physiological or pathological feature which in a way obstructs free drainage from the sinuses, permits the stasis of secretion and thus predisposes to infection. Knowing these features, many factors have been described as playing a role in the development of chronic sinusitis. These include allergy, asthma, dental disease, nasal polyps, immunodeficiency, mucociliary disorders, trauma, medications, surgery, noxious chemicals and micro-organisms (viral, bacterial and fungal), anatomic abnormalities such as a septal deviation, concha bullosa, septal spur or paradoxical turbinate [103]. Allergy being possibly more prevalent in CRSwNP compared with CRSsNP was observed in several studies as well as in ours. Those studies have demonstrated an increased prevalence for perennial allergies in patients with CRSwNP compared with controls, with reports varying between 45% to 77.4% [104-108]. Additionally, 2 studies showed a strong association between perennial allergies and CRSwNP with odds ratios of 2.69 and 6.0 described. [104,108]. In our study, association with allergies is not prevalent which was encountered in only 23% of patients with CRSwNP and 18% of patients with CRSsNP, however, it showed higher incidence than in general population. Moreover, there is a higher prevalence of CRS among patients with asthma, and the presence of CRS is associated with poor asthma outcomes, especially with CRSwNP [109-112]. Compared to patients who do not have asthma, patients with asthma and CRS have poorer outcomes, less quality of life improvement, and a higher rate of revision surgery after ESS [113,114]. In our study, 10% of patients with CRSwNP and 5% of patients with CRSsNP have asthma. Lastly, besides allergies and asthma, we need to mention that out of 100 patients 17% with CRS had septal deformation (4%-CRSwNP, 13%-CRSsNP). There are three theories explaining the relation between the nasal septal deviation and chronic rhinosinusitis. The first one is the mechanical theory, which states that secretions accumulate in the sinus as a result of narrowing of the ostiomeatal complex and thus infections ensue in the retained secretions and cause chronic rhinosinusitis. The second theory is the aerodynamic theory according to which the mucociliary activity decreases following the nasal flow rate increase and mucosal dryness in relation with the nasal septal deviation and consequently,

chronic rhinosinusitis develops. Final theory is the Bachert's pressure theory. According to this theory, deviation of the posterior nasal septum causes chronic rhinosinusitis by creating pressure and air flow changes within the maxillary sinuses [113,115].

9. Conclusion

We hypothesized that a significant proportion of patients with CRS have asthma or allergy of any kind.Since almost every second patient has an allergy (41%) and 15 % have asthma we can conclude that there is a higher prevalence of those comorbidities in patients having CRS than in general population. Moreover, we have to put emphasis on 65% of male patients in our study, as well as on FESS with polipectomy being the dominant type of surgical procedure (42%). Lastly, 17% of patients underwent septoplasty due to nasal septal deformity which could play a role in ethiopathogenesis of CRS.

Acknowledgements

First, I would like to thank my mentor, prof. dr. sc. Tomislav Baudion. His knowledge, patience and kindness guided me throughout the process of writing this thesis, for which I will always be grateful. I would also like to thank my dearest friends, especially Zrinka, for always being by my side, motivating, and encouraging me. Finally, I would like to thank my family for their endless support, I would not be me without you.

References

1. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl. 2007(20):1-136.
2. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clinic proceedings Mayo Clinic. 2011 May;86(5):427-43.
3. Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Journal of otolaryngology - head & neck surgery = Le Journal d'otorhino-laryngologie et de chirurgie cervicofaciale. 2011 May;40 Suppl 2:S99-193.
4. Chan Y, Kuhn FA. An update on the classifications, diagnosis, and treatment of rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2009 Jun;17(3):204-8.
5. Marple BF, Brunton S, Ferguson BJ. Acute bacterial rhinosinusitis: A review of U.S. treatment guidelines. Otolaryngology - Head & Neck Surgery. [Review]. 2006;135(3):341-8. Sasama J, Sherris DA, Shin SH, Kephart GM, Kern EB, Ponikau JU. New paradigm for the roles of fungi and eosinophils in chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2005 Feb;13(1):2-8.
6. Ponikau JU, Sherris DA, Kern EB, Homburger HA, Frigas E, Gaffey TA, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clinic proceedings Mayo Clinic. 1999 Sep;74(9):877-84
7. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: Inflammation. The Journal of allergy and clinical immunology. 2011.
8. Roca-Ferrer J, Garcia-Garcia FJ, Pereda J, Perez-Gonzalez M, Pujols L, Alobid I, et al. Reduced expression of COXs and production of prostaglandin E(2) in patients with nasal polyps with or without aspirin-intolerant asthma. The Journal of allergy and clinical immunology. 2011 Jul;128(1):66-72 e1.
9. Butterworth-Heinemann; oxford, 7th edn; 2008:13185. Bachert C, Zhang N, Patou J, van Zele T, Gevaert P. Role of staphylococcal superantigens in upper airway disease. Curr Opin Allergy Clin Immunol. 2008 Feb;8(1):34-8.

10. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. The Journal of allergy and clinical immunology. 2001 Apr;107(4):607-14.
11. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2009 Jul;124(1):37-42.
12. Kern RC, Conley DB, Walsh W, Chandra R, Kato A, Tripathi-Peters A, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. American journal of rhinology. 2008 Nov-Dec;22(6):549-59.
13. Foreman A, Holtappels G, Psaltis AJ, Jervis-Bardy J, Field J, Wormald PJ, et al. Adaptive immune responses in Staphylococcus aureus biofilm-associated chronic rhinosinusitis. Allergy. 2011 Aug 11;66(11):1449-56.
14. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. Aust Dent J. 2009 Sep;54 Suppl 1:S2-10.
15. Collins JG, Blackwell DL, Tonthat L, Shashy RG, Moore EJ, Weaver A, et al. Prevalence of selected chronic conditions: United States, 1990-1992 Summary health statistics for the U.S. population: National Health Interview Survey, 1997 Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota.
16. The role of nasal endoscopy in outpatient management. Vital Health Stat 10.1997;130(194):1-89. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. Vital Health Stat 10. 2002 May(205):1-109.
17. Shashy RG, Moore EJ, Weaver A. Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota. Archives of otolaryngology--head & neck surgery. 2004 Mar;130(3):320-3.
18. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA(2)LEN study. Allergy. 2011 Sep;66(9):1216-23.
19. El Hasnaoui A, Jankowski R, Serrano E, Pribil C, Neukirch F, Klossek JM. Evaluation of a diagnostic questionnaire for nasal polyposis: an observational, cross-sectional study. Rhinology. 2004 Mar;42(1):1-7.

20. Hadfield PJ, Rowe-Jones JM, Mackay IS. The prevalence of nasal polyps in adults with cystic fibrosis. Clinical otolaryngology and allied sciences. 2000 Feb;25(1):19-22.
21. Settipane GA. Epidemiology of nasal polyps. Settipane G LV, Bernstein JM, Tos M, editor. Rhode Island: Oceanside Publications; 1997.
22. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy. 1971 Dec;29(12):631-4.
23. Chafee FH. Aspirin intolerance. I. Frequency in an allergic population. Allergy Clin Immunol. 1974(53):193-9.
24. Webe r RW, Hof fman M, R a ine DA, Jr., Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. The Journal of allergy and clinical immunology. 1979 Jul;64(1):32-7.
25. Szczeklik A, Gryglewski RJ, Czerniawska- My sik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. The Journal of allergy and clinical immunology. 1977 Nov;60(5):276-84.
26. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. The Journal of allergy and clinical immunology. 1979 Dec;64(6 Pt 1):500-6.
27. Ogino S. Aspirin-induced asthma and nasal polyps. Acta Otolaryngo lSuppl. 1986(430):21-7.
28. May A, Wagner D, Langenbeck U, Weber A. [Family study of patients with aspirin intolerance and rhinosinusitis]. HNO. 2000 Sep;48(9):650-4.
29. Chee L, Graham SM, Carothers DG, Ballas ZK. Immune dysfunction in refractory sinusitis in a tertiary care setting. The Laryngoscope. 2001 Feb;111(2):233-5.
30. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science (New York, NY). 1989 Sep 8;245(4922):1066-73.
31. E l legard EK. The etiology and management of pregnancy rhinitis. Am J Respir Med. 2003;2(6):469-75.
32. Zinreich SJ, Mattox DE, Kennedy DW, Chisholm HL, Diffley DM, Rosenbaum AE. Concha bullosa: CT evaluation. J Comput Assist Tomogr. 1988 Sep-Oct;12(5):778-84.

33. Jones NS. CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings. Clinical otolaryngology and allied sciences. 2002 Feb;27(1):11-
34. Jones NS, Strobl A, Holland I. A study of the CT findings in 100 patients with rhinosinusitis and 100 controls. Clinical otolaryngology and allied sciences. 1997 Feb;22(1):47-
35. Willner A, Choi SS, Vezina LG, Lazar RH. Intranasal anatomic variations in pediatric sinusitis. American journal of rhinology. 1997 Sep-Oct;11(5):355-60.
36. Gordts F, Clement PA, Buisseret T. Prevalence of sinusitis signs in a non-ENT population. ORL J Otorhinolaryngol Relat Spec. 1996 Nov-Dec;58(6):315-9.
37. Dykewicz MS. 7. Rhinitis and sinusitis. The Journal of allergy and clinical immunology. 2003 Feb;111 (2 Suppl):S520-9.
38. Damm M, Quante G, Jungehuelsing M, Stennert E. Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. The Laryngoscope. 2002 Feb;112(2):310-5.
39. Ling FT, Kountakis SE. Important clinical symptoms in patients undergoing functional endoscopic sinus surgery for chronic rhinosinusitis. The Laryngoscope. 2007 Jun;117(6):1090-3.
40. West B, Jones NS. Endoscopy-negative, computed tomography-negative facial pain in a nasal clinic. The Laryngoscope. 2001 Apr;111(4 Pt 1):581-6.
41. Litvack JR, Fong K, Mace J, James KE, Smith TL. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. The Laryngoscope. 2008 Dec;118(12):2225-30.
42. Craig TJ, Ferguson BJ, Krouse JH. Sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. Am J Otolaryngol. 2008 May-Jun;29(3):209-17.
43. Rombaux P, Liistro G, Hamoir M, Bertrand B, Auber t G, Verses T, et al. Nasal obstruction and its impact on sleep related breathing disorders. Rhinology. 2005 Dec;43(4):242-50.
44. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). The Journal of allergy and clinical immunology. 2009 Sep;124(3):428-33.

45. Storms W, Yawn B, Fromer L. Therapeutic options for reducing sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. Current medical research and opinion. 2007;23(9):2135-4637. Collins JG, Blackwell DL, Tonthat L, Shashy RG, Moore EJ, Weaver A, et al. Prevalence of selected chronic conditions: United States, 1990-1992 Summary health statistics for the U.S. population: National Health Interview Survey, 1997 Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota the role of nasal endoscopy in outpatient management. Vital Health Stat 10. 1997;130(194):1-89.
46. Meltzer EO, Hamilos DL, Hadley JA. Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg* 2004;131:S1 S62.
47. Benninger MS, Anon J, Mabry RL. The medical management of rhinosinusitis. *Otolaryngol Head Neck Surg* 1997;117:S41–S49.
48. Lund VJ. Maximal medical therapy for chronic rhinosinusitis. *Otolaryngol Clin North Am*2005;38:1301–1310.
49. Grzincich G, Capra L, Cammarata MG, Spaggiari C, Pisi G. Effectiveness of intranasal corticosteroids. *Acta Biomed.* 2004;75:22–25.
50. Gillespie MB, Osguthorpe JD. Pharmacologic management of chronic rhinosinusitis, alone or with nasal polyposis. *Curr Allergy Asthma Rep* 2004;4:478–485.
51. Badia L, Lund V. Topical corticosteroids in nasal polyposis. *Drugs* 2001;61:573–578.
52. Langrick AF. Comparison of flunisolide and beclomethasone dipropionate in seasonal allergic rhinitis. *Curr Med Res Opin* 1984;9:290–295
53. Dingsor G, Kramer J, Olsholt R, Soderstrom T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. *Rhinology* 1985;23:49–58.
54. DeMarcantonio MA, Han JK. Systemic therapies in managing sinonasal inflammation. *Otolaryngol Clin North Am* 2010;43:551–563, ix.
55. Lennard CM, Mann EA, Sun LL, Chang AS, Bolger WE. Interleukin-1 beta, interleukin-5, interleukin-6, interleukin-8, and tumor necrosis factor-alpha in chronic sinusitis: response to systemic corticosteroids. *Am J Rhinol* 2000;14:367–373.
56. Van Camp C, Clement PA. Results of oral steroid treatment in nasal polyposis. *Rhinology* 1994;32:5–9.

57. Harvey RJ, Schlosser RJ. Local drug delivery. *Otolaryngol Clin North Am* 2009;42:829–845
58. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. *Laryngoscope* 1997;107:500–550.
59. Yu C, Chen FDY, Wang J, Gu YJ, Gao X. Effect of Pulmicort Respule on rehabilitation after functional endoscopic sinus surgery. *Acta Chimi Sin* 2007;21:100–102.
60. Kennedy DW. Functional endoscopic sinus surgery. Technique. *Arch Otolaryngol* 1985;111:643–649.
61. Poetker DM, Mendolia-Loffredo S, Smith TL. Outcomes of endoscopic sinus surgery for chronic rhinosinusitis associated with sinonasal polyposis. American journal of rhinology. 2007 Jan-Feb;21(1):84-859.
62. Dalziel K, Stein K, Round A, Garside R, Royle P. Systematic review of endoscopic sinus surgery for nasal polyps. Health Technol Assess. 2003;7(17):iii, 1-159.
63. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. The Laryngoscope. 2004 May;114(5):811-3.
64. Hopkins C, Browne JP, Slack R, Lund V, Topham J, Reeves B, et al. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Clin Otolaryngol. 2006 Oct;31(5):390-8.
65. Article title: Complications of Sinus Surgery. Website title: American Rhinologic Society. Taken on 25.5.2018. Link:http://care.american-rhinologic.org/complications_ess.
66. Kaliner M. Treatment of sinusitis in the next millennium. Allergy and asthma proceedings: the official journal of regional and state allergy societies. 1998 Jul-Aug;19(4):181-4.
67. Krause HF. Allergy and chronic rhinosinusitis. Otolaryngology - Head & Neck Surgery. 2003;128(1):14-6.
68. Jones NS, Carney AS, Davis A. The prevalence of allergic rhinosinusitis: a review. J Laryngol Otol. 1998 Nov;112(11):1019-30.
69. Bailey B. The impact of pollution on the upper alimentary and respiratory tracts. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1992(106):736-40.
70. Stammberger H. Functional endoscopic sinus surgery. Philadelphia: B.C. Decker; 1991.

71. Benninger MS. Rhinitis, sinusitis and their relationships to allergies. American journal of rhinology. 1992;6:37-43
72. Savolainen S. Allergy in patients with acute maxillary sinusitis. Allergy. 1989 Feb;44(2):116-22
73. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2000 Dec;123(6):687-91.
74. Grove R. Chronic hyperplastic sinusitis in allergic patients: a bacteriologic study of 200 operative cases. The Journal of allergy and clinical immunology. 1990(11):271-6.
75. Karlsson G, Holmberg K. Does allergic rhinitis predispose to sinusitis? Acta Otolaryngol Suppl. 1994;515:26-8; discussion 9.
76. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012 Jan;67(1):91-8.
77. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? The Journal of allergy and clinical immunology. 2003 Nov;112(5):877-82.
78. Matsuno O, Ono E, Takenaka R, Okubo T, Takatani K, Ueno T, et al. Asthma and sinusitis: association and implication. Int Arch Allergy Immunol. 2008;147(1):52-8.
79. Salvin RG, Cannon RE, Friedman WH, Palitang E, Sundaram M. Sinusitis and bronchial asthma. The Journal of allergy and clinical immunology. 1980 Sep;66(3):250-7.
80. Schwartz HJ, Thompson JS, Sher TH, Ross RJ. Occult sinus abnormalities in the asthmatic patient. Arch Intern Med. 1987 Dec;147(12):2194-698. Brown S. Anatomy of nose and paranasal sinuses. In: Lund VJ, H Stammberger, Scott Brown Otolaryngology, Basic Sciences;
81. Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its Impact on Asthma. The Journal of allergy and clinical immunology. 2001;108(5 Suppl):S147-334.
82. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: A crosssectional, case-control study. Allergy. 2005;60(2):233-7.

83. Downing E. Bronchial reactivity in patients with nasal polyposis before and after polypectomy. The Journal of allergy and clinical immunology. 1982;69(2):102.

84. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 2000 Sep;16(3):432-6.
85. Larsen K. The clinical relationship of nasal polyps to asthma. Settipane G LV, Bernstein JM, Tos M, editor. Rhode Island: Oceanside Publications; 1997.
86. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? The Journal of allergy and clinical immunology. 2003 Nov;112(5):877-82.
87. Hamilos DL, Leung DY, Wood R, Cunningham L, Bean DK, Yasruel Z, et al. Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. The Journal of allergy and clinical immunology. 1995 Oct;96(4):537-44.
88. Ragab A, Clement P, Vincken W. Correlation between the cytology of the nasal middle meatus and BAL in chronic rhinosinusitis. Rhinology. 2005 Mar;43(1):11-7.
89. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012 Jan;67(1):91-8.
90. Kountakis SE, Bradley DT. Effect of asthma on sinus computed tomography grade and symptom scores in patients undergoing revision functional endoscopic sinus surgery. American journal of rhinology. 2003 JulAug;17(4):215-9.
91. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. The Journal of allergy and clinical immunology. 2002 Apr;109(4):621-6.
92. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA(2)LEN study. Allergy. 2011 Sep;66(9):1216-23.90.

93. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67(1):91–98. doi: 10.1111/j.1398-9995.2011.02709.x
94. Kim YS, Kim NH, Seong SY, Kim KR, Lee GB, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in Korea. Am J Rhinol Allergy. 2011;25(3):117–121. doi: 10.2500/ajra.2011.25.3630.
95. Hamilos DL. Chronic rhinosinusitis: Epidemiology and medical management. J Allergy Clin Immunol. 2011;128(4):693–707. doi: 10.1016/j.jaci.2011.08.004.
96. Pilan RR, Pinna FR, Bezerra TF, Mori RL, Padua FG, Bento RF, Perez-Novo C, Bachert C, Voegels RL. Prevalence of chronic rhinosinusitis in Sao Paulo. Rhinology. 2012;50(2):129–138.
97. Slavin RG, Spector SL, Bernstein IL, Kaliner MA, Kennedy DW, Virant FS. American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6 Suppl):S13–S47. doi: 10.1016/j.jaci.2005.09.048.
98. Rosenfeld RM. Clinical practice guideline on adult sinusitis. Otolaryngol Head Neck Surg. 2007;137(3):365–377. doi: 10.1016/j.otohns.2007.07.02
99. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol. Head Neck Surg. 1997;117:S1–S7. doi: 10.1016/S0194-5998(97)70001-9
100. Fokkens W, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl 2007;20:1–36.
101. Bugten V, Nordgård S, Romundstad P, Steinsvåg S. Chronic rhinosinusitis and nasal polyposis; indicia of heterogeneity. Rhinology. 2008;46(1):40-44.
102. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. Laryngoscope 2008;118:1521–7.
103. Tan BK, Zirkle W, Chandra R, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. Int Forum Allergy Rhinol 2011;1:88–94.
104. Asero R, Bottazzi G. Hypersenstivity to molds in patients with nasal polyposis: a clinical study. J Allergy Clin Immunol 2000;105:186–8.

105. Asero R, Bottazzi G. Nasal polyposis: a study of its association with airborne allergen hypersensitivity. Ann Allergy Asthma Immunol 2001;86:283–5.

106. Pumhirun P, Limitlaohapanth C, Wasuwat P. Role of allergy in nasal polyps of Thai patients. Asian Pac J Allergy Immunol 1999;17:13–5.

107. Rosati MG, Peters AT. Relationships among allergic rhinitis, asthma, and chronic rhinosinusitis. *Am J Rhinol Allergy 2016; 30:44-47.*

108. Dixon AE. Rhinosinusitis and asthma: the missing link. *Curr Opin Pulm Med 2009; 15:19-24.*

109. Habib AR, Javer AR, Buxton JA. A population-based study investigating chronic rhinosinusitis and the incidence of asthma. Laryngoscope 2016; 126:1296-302.

110. Ek A, Middelveld RJ, Bertilsson H, et al. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA(2)LEN survey. Allergy 2013; 68:1314-1321.

111. Loehrl TA, Ferre RM, Toohill RJ, et al. Long-term asthma outcomes after endoscopic sinus surgery in aspirin triad patients. *Am J Otolaryngol* 2006; 27:154–160.

112. Chen FH, Zuo KJ, Guo YB, et al. Long-term results of endoscopic sinus surgery-oriented treatment for chronic rhinosinusitis with asthma. *Laryngoscope* 2014; 124:24–28.

113. Brown S. Anatomy of nose and paranasal sinuses. In: Lund VJ, H Stammberger, Scott Brown Otolaryngology, Basic Sciences; 5, Butterworth-Heinemann; oxford, 7th edn; 2008:1318.

114. Adrian Drake-Lee “the physiology of the Nose and Paranasal sinuses” Scott Brown’s Otolaryngology. 6th edition, Volume 1, Basic sciences 1,6,11-15.

115. Kim YS, Kim NH, Seong SY, Kim KR, Lee GB, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in Korea. Am J Rhinol Allergy. 2011;25(3):117–121. doi: 10.2500/ajra.2011.25.3630

Biography

Nika Puževski was born on October 12, 1994 in Zagreb, Croatia. During her primary school she also attended and finished 6-year music school. Her decision to enroll into University of Zagreb, School of medicine grew during high school, which she did in July 2013. During study, she worked as a student demonstrator in the course History taking and physical education on the hematology department at Hospital Center Dubrava under the mentorship of dr. Zdravko Mitrović. Once graduating in 2019, she is looking forward to gain the experience and to start working.