**How to Cite**:
Moazen, E. M., Salama, K. S. M., Boghdady, M. H. A., & Sayed, D. M. E. (2021). Assessment of coexistence of subclinical bronchial asthma in patients with allergic nasal polyposis refractory to medical therapy. *International Journal of Health Sciences*, *5*(S2), 1101–1117. https://doi.org/10.53730/ijhs.v5nS2.14153

# Assessment of coexistence of subclinical bronchial asthma in patients with allergic nasal polyposis refractory to medical therapy

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***Abstract*---**Background: Coexistence of bronchial asthma and allergic nasal polyposis make both disorders more difficult to control with more exacerbation and more eosinophilic inflammation. Aim: to assess the coexistence of subclinical bronchial asthma in patients with allergic nasal polyp refractory to medical therapy and to identify those at risk of developing asthma. Subjects and methods: A case-control study was conducted on 60 allergic nasal polyp patients and 60 healthy subjects. All of them were assessed by peripheral eosinophils%, allergic rhinitis score (SFAR), NOSE-score, endoscopic-sinus examination, sinus computed tomography using Lund and Mackey scoring-system, asthma screening questionnaire (ASQ), spirometric-indices, and histopathological examination of endoscopically removed polyps. Results: Patients with allergic nasal polyps had significantly lower spirometric-indices than controls. Subclinical asthma was significantly more common in-patient group than controls (61.7% vs. 10%), it was of mild and moderate severity (83.8% and 16.2%). Allergic nasal polyp patients with coexistence of asthma had significantly higher peripheral eosinophils %, SFAR-score, NOSE-score, Lund and Mackey CT-score, and ASQ score (10, 39.7, 40.5, 40, and 40.1) than patients without asthma (15.2, 15.7, 15.2

and14.1). Moreover, they had significantly common eosinophilic-predominate pathological subtypes (81.1%). All spirometric indices ($FEV_1$/FVC ratio, $FEV_1$%, FVC% and FEF %) were negatively correlated with SAFR-score, ASQ-score, NOSE-score, Lund and Mackey CT-score, blood eosinophil %, and endoscopic-score ($p< 0.05$). The most significant risk factors of asthma in patients with allergic polyp were smoking (OR=4.76), male sex (OR=4.6), higher SAFR-score (OR=0.21), eosinophils % (OR=0.049), and Lund and Mackey CT-score (OR=0.54). The ASQ had 97.3% sensitivity, 95.6% specificity, 95.7% PPV and 97.3% NPV in diagnosing asthma inpatients with allergic nasal polyp. Conclusions: Undiagnosed asthma is common among patients with allergic nasal polyposis refractory to medical therapy especially in smokers' males with higher SAFR-score, eosinophils %, and Lund and Mackey CT-score. The ASQ had very good sensitivity, specificity, PPV and NPV to diagnose asthma in patients with allergic nasal polyp.

***Keywords*---**asthma, bronchial asthma, allergic nasal polyp, united airway diseases.

## Introduction

Chronic rhinosinusitis (CRS) has been defined as a persistent inflammatory response involving the mucous membranes of the nasal cavity and paranasal sinuses. CRS can be classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) (Fokkens et al., 2012). CRSwNP has a negative impact on patients' quality of life, not only due to discomfort of specific symptoms e.g. chronic rhinorrhea, nasal obstruction, facial pressure and hyposmia, but also due to general dysfunction manifested as fatigue and loss of sleep, which may further cause cognitive impairment or depression. Asthma is a disease of many variations characterized by chronic airway inflammation. It has two defining features; first is history of respiratory symptoms as wheeze, chest tightness, cough and shortness of breath that vary over time and in intensity and the second is variable expiratory airflow limitation (GINA 2020). Both asthma and allergic rhinitis are presenting with numerous phenotypes and are considered the most frequent chronic inflammation of both upper and lower airways (Vennilavan et al., 2022).

The immuno-physiological characteristics of upper and lower airway diseases are similar, and both sites have similar anatomical structures. The presence of inflammatory upper airway disease may influence the pathological condition of some lower airway diseases (Bousquet et al., 2012). Patients with CRSwNP often have coexisting asthma under the concept of "United Airway Disease", which is one of the most challenging phenotypes to treat (Langdon and Mullol ., 2016). Asthma in the presence of nasal polyposis is also more difficult to control, being more exacerbation prone, with increased airway obstruction and extensive eosinophilic inflammation (Laidlaw et al., 2021). Early diagnosis of asthma in patient with CRwNP is very important to improve patient's control. Therefore, this study was conducted to assess the coexistence of subclinical bronchial asthma in

patients with allergic nasal polyp refractory to medical therapy and to identify those at risk of developing asthma.

**Materials and Methods**

This case-control study was conducted at chest and pathology diseases departments, Al-Zahraa university hospital and otorhinolaryngology department of Al-Sayed Galal university hospital during the period from August 2021 to March 2022. The sample size was calculated by Epi info, Atlanta, Georgia (US) according to the annual flow of allergic rhinitis cases and itsprevalence in Egypt 3.6% (Al-Digheari et al., 2018) with margin of error 5% and confidence level of 95% and it was found to be 54 cases. A total of 187 patients presented with clinical picture suggestive of allergic nasal polyps were evaluated for study eligibility.

One hundred twenty-seven (127) patients were non-eligible and excluded from the study while 60 patients were eligible and enrolled into the study (figure 1). Moreover, 60 age and sex-matched healthy subjects were enrolled as a control group. Patients with non-allergic nasal polyp, allergic rhinitis without polyp, those who were unable to perform spirometry and those who were previously diagnosed and treated for asthma were excluded from the study (figure 1). An informed written consent was gotten from every participants before enrolment into the study in concordance with the declaration of Helsinki. The study was approved by the ethical committee of faculty of medicine for girls, Cairo, Al-Azhar University, Egypt (IRB 202106861).

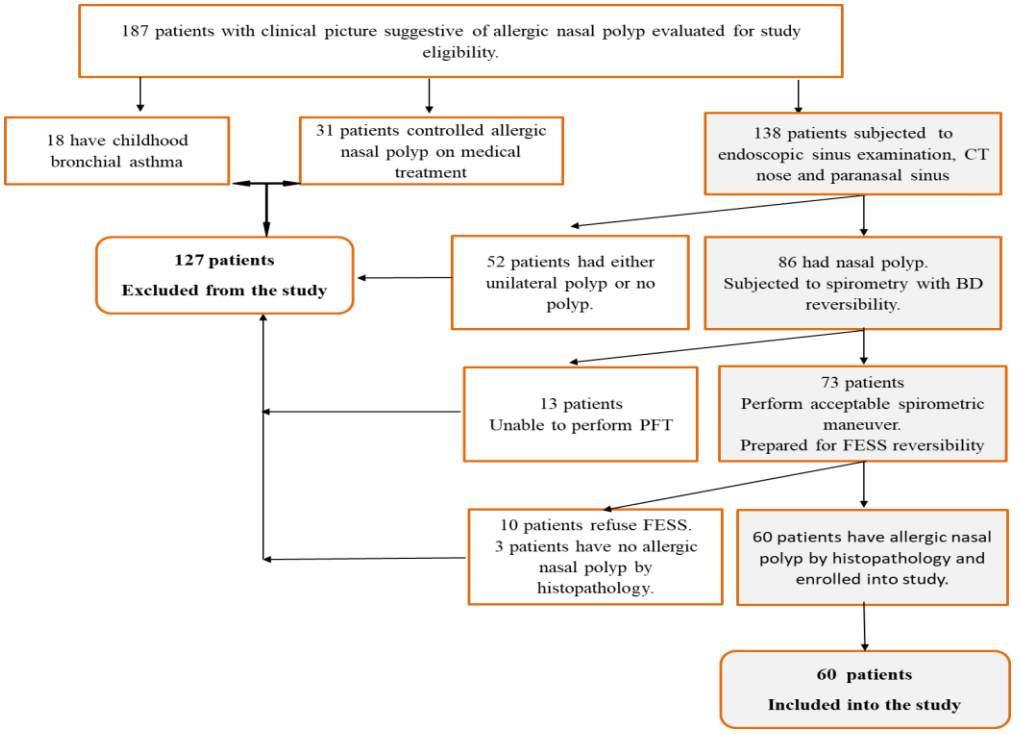


Figure (1): Flowchart for patients inclusion into the study

Detailed history was taken including age, sex, and smoking status. The diagnoses of allergic nasal polyps was made based on symptoms severity using questionnaires and nasal obstruction symptom evaluation (NOSE), peripheral esinophils %, endoscopic sinus examination, computed tomography (CT) scan of nose and paranasal sinuses, and pathological examination of sinoscopically removed polyp.

We used an Arabic version of the score for allergic rhinitis (SFAR), a simple self-reporting tool with a cut-off point of 7 (Alharethy et al., 2017). Blood esinophils % was done using a hematological analyzer (Sysmex XE-21N, Kobe, Japan). The NOSE-scale was used to assess the severity of nasal obstruction, using five questions, each scored on a scale of 0 to 4. The total NOSE-score was converted to a 100-point scale, which defines nasal obstruction severity using a classification system: mild (5-25), moderate (30-50), severe (55-75), or extreme (80-100) (Clark et al.,2018).

Endoscopic examinations were done using Karlstorz nasal sinoscope 0 degree (Germany). After applying topical anesthesia and topical decongestant. The nasal cavity was carefully examined for presence of nasal polyps and its evaluation according to the Meltzer clinical scoring system. The Meltzer clinical scoring system is a 0-4 polyp grading system (0 = no polyps, 1 = polyps confined to the middle meatus, 2 = multiple polyps occupying the middle meatus, 3 = polyps extending beyond middle meatus, 4 = polyps completely obstructing the nasal cavity) (Meltzer et al., 2011) (figure 2).

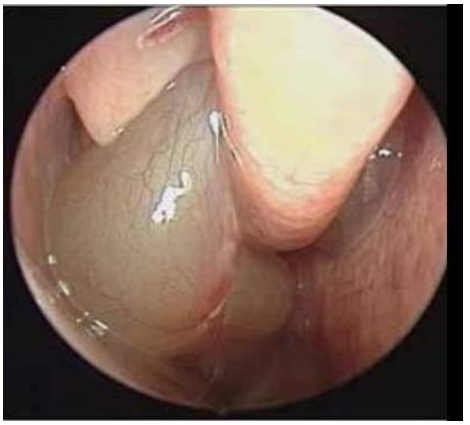

Figure (2): Endoscopic view of the Rt. nasal cavity shows large polypoidal glistening grape like soft tissue filling middle meatus and protruding inside nasal cavity mostly grade 4 allergic nasal polyp

High resolution CT evaluation of the paranasal sinuses was performed in the preoperative period using multidetector scanner (160 detectors) (Toshiba, Prime Aquilion Japan) (figure 3). Lund and Mackey radiological staging system was applied, with thin one mm axial sections with both coronal and axial sections reconstruction. This score ranges from 0 (complete lucency of all sinuses) to 24 (complete opacification of all sinuses) (Lund and Mackey.,1994) (figure 3).

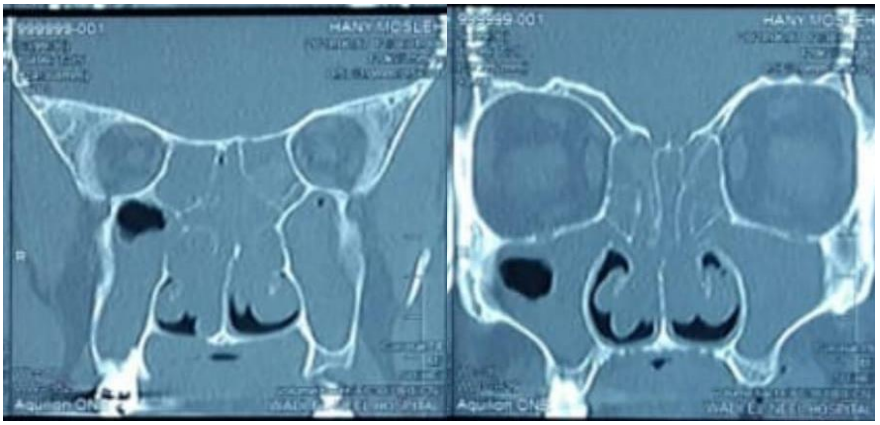

Figure (3): ÇT nose and paranasal sinuses coronal cuts bone window shows bilateral radio opaque opacities filling all sinuses and occluding nasal cavity. No orbital or skull base invasion. Mostly allergic sinonasal polyposis

The diagnosis of bronchial asthma was done in 2 step; first step by screening the participants using an asthma screening questionnaire (ASQ). ASQ is a simplified 6-item questionnaire developed based on common questions used at clinics affiliated with the university of South Florida, and in recommendations from the national asthma education and prevention program and the global initiative for asthma. After patients had completed the questionnaire, a physician administered the same questionnaire to ensure that all questions had a response and to clarify any uncertainties. The questionnaire consists of 6 questions in a yes/no answer format. Questions 1 and 2 evaluate cough, whereas question 6 address 4 dimensions of asthma symptoms including cough, chest tightness, wheeze, and shortness of breath in 4 commonly related provoking conditions. All questions have an equivalent weight of 1 point except for the first 2 questions, which have 2 points each. A total ASQ score was calculated as the sum of all positive responses, ranging from 0-20 (Shin et al.,2010).

The second step was the confirmation of asthma diagnosis by conducting spirometry using (MEDISOFT-HYPERAIR compact +flow meter pulmonary function Testing-Belgium). It was performed according to American Thoracic Society guidelines. The following indices were recorded forced expiratory volume in the first second ($FEV_1$%), forced vital capacity (FVC%), $FEV_1$/FVC ratio and forced expiratory flow 25-76% (FEF25-75%). Spirometric-indices were calculated using best out of three technically satisfactory trials in accordance with ATS guidelines (Miller MR et al., 2005).

To establish reversibility the participants were inhaled two puffs of salbutamol (400 µg) and an improvement in $FEV_1$ of ≥12% and ≥200 mL was considered positive and bronchial asthma diagnosis was established. Additionally, asthma severity was assessed according to (GINA, 2020). The studied were divided based on ASQ and spirometry into two groups; allergic nasal polyp with asthma group and allergic nasal polyp without asthma group. Patients with allergic nasal polyp underwent functional endoscopic sinus surgery (FESS) performed at the Otorhino-laryngology department, Al-Sayed Galal university hospital, Cairo, Al-

Azhar university, Egypt and the biopsies were examined by experienced pathologist author.

**Statistical analysis**

Data was statistically analyzed by the Statistical Package for Social Science (SPSS) program version 17.0 (SPSS Inc., Chicago, USA). The Shapiro-Wilk test was used for testing normality of the studied variables. Descriptive analysis was done for each item and the results were expressed as median with interquartile range (IQR) for non-parametric data, and as percentages for nominal data. Comparisons to assess the difference between the groups were done using the Chi-square ($X^2$) test for qualitative data and by Mann Whitney for non-parametric data. Multivariate logistic regression analysis was used to identify the most significant risk factors predictive of bronchial asthma in patients with allergic nasal polyp. Odds ratios (ORs) with 95% confidence intervals were calculated for the evaluation of the overall association between each possible risk factor and the occurrence predictive for the isolation of asthma in patients with allergic nasal polyp. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ASQ in diagnosis of asthma among patients with allergic nasal polyp was calculated. Statistical significance was considered at a probability p value ( p value) <0.05 (with a confidence limit at 95%).

**Results**

Table (1) shows that the SFAR was statistically significantly higher in patients with allergic nasal polyp compared to controls (mean rank 33.65 vs.13.4, p 0.003). There was significant increase of peripheral esinophils % in patients with allergic nasal polyp than controls (mean rank 86.1% vs. 21.1%, p 0.001). Allergic nasal polyp patients had statistically significant higher ASQ score compared to controls (mean rank 81.4 vs.39.5, p 0.001). Patients with allergic nasal polyp had significantly lower $FEV_1$\ FCV ratio, $FEV_1$%, FVC% and FEF 25-75% (mean rank 44.7, 50.3, 37.9 and 40.7 respectively) compared to controls (mean rank 76.36, 70.6, 83.1, and 80.1 respectively) (p 0.001). Accordingly, patients with allergic nasal polyp had significantly higher frequencies of coexistence of subclinical bronchial asthma than controls (61.7% vs. 10%, p0.001). Asthma was of mild and moderate severity in patients group (83.8% and 16.2% respectively), and it was of mild severity in control group (p 0.031).

Table (1): Comparison of studied variables between allergic nasal poly group and control group

| Items | | Allergic nasal poly (n = 60) | Control (n = 60) | Stat. test | P-value |
|---|---|---|---|---|---|
| Age/yrs. | Median (IQR) | 39 (32 – 49) | 38 (34 - 45.8) | MW = 1762 | 0.842 |
| | Mean rank | 61.1 | 59.9 | | |
| Sex | Male | 41 (68.3%) | 36 (60%) | $X^2$ = 0.9 | 0.341 |
| | Female | 19 (31.7%) | 24 (40%) | | |
| Smoking | Smokers | 32 (53.3%) | 34 (56.7%) | $X^2$ = 0.13 | 0.714 |
| | Non-smokers | 28 (46.7%) | 26 (43.3%) | | |

| | | | | | |
|---|---|---|---|---|---|
| Eosinophil% | Median (IQR) | 3.3 (2.3- 4.55) | 0.99 (0.87-1.3) | MW = 51 | 0.001 * |
| | Mean rank | 89.6 | 31.3 | | |
| SFAR-score | Median (IQR) | 10 (9.2-11.2) | 8 (7 – 9) | MW=44.5 | 0.002 * |
| | Mean rank | 33.3. | 13.4. | | |
| NOSE-score | Median (IQR) | 12 (9 – 13) | 1 (0 – 1) | - | - |
| | Mean rank | 90.5 | 30.5 | | |
| Endoscopic sinus-score | Grade 1 | 9 (15%) | 60 (100%) | - | - |
| | Grade 2 | 18 (30%) | 0 (0%) | | |
| | Grade 3 | 22 (36.7%) | 0 (0%) | | |
| | Grade 4 | 11 (18.3%) | 0 (0%) | | |
| Lund and Mackey CT-score | Median (IQR) | 17 (14.3 – 20) | 17 (14.3 – 20) | - | - |
| | Mean rank | 90.5 | 90.5 | | |
| ASQ-score | Median (IQR) | 11 (3 – 12) | 1 (0 – 2) | MW=542.5 | 0.001 * |
| | Mean rank | 81.4 | 39.5 | | |
| $FEV_1$/FVC ratio | Median (IQR) | 76(70.3 – 85) | 87(85.3 – 88) | MW= 852 | 0.001 * |
| | Mean rank | 44.7 | 76.3 | | |
| $FEV_1$% | Median (IQR) | 73(66 – 84) | 82(80 – 85) | MW=1192 | 0.001 * |
| | Mean rank | 50.3 | 70.6 | | |
| FVC% | Median (IQR) | 76(73 - 79.8) | 83(80 – 85) | MW=444 | 0.001 * |
| | Mean rank | 37.9 | 83.1 | | |
| FEF 25-75% | Median (IQR) | 62.5(57.3 - 67.9) | 69.5(68 – 71) | MW= 610 | 0.001 * |
| | Mean rank | 40.7 | 80.3 | | |
| Bronchial asthma | Yes | 37 (61.7%) | 6 (10%) | $X^2$ = 34.8 | 0.001 * |
| | No | 23 (38.3%) | 54 (90%) | | |
| Asthma severity | Mild | 31 (83.8%) | 6 (100%) | $X^2$ = 0.99 | 0.031 * |
| | Moderate | 6 (16.2%) | 0 (0%) | | |

MW: Mann Whitney U test, $X^2$: Chi-square test, *: Significant p-value

Table (2) demonstrates that allergic nasal polyp patients with coexistent asthma were significantly males and smokers (81.1% and 67.6%, respectively) compared to those without asthma (47.8% and 30.4% respectively) ($p< 0.05$). Moreover, they had statistically significant higher peripheral esinophils %, SFAR score and NOSE score (mean rank 40, 39.7 and 40.5 respectively) compared to patients without asthma (mean rank 15.2 ,15.7 and 14.4 respectively (p 0.001 each). Most of allergic nasal polyp patients with asthma had polyps extending beyond middle meatus (56.8%), while those without asthma had polyps confined to the middle meatus (39.1%) (p 0.003). Allergic nasal poly patients with asthma had statistically significant higher Lund and Mackey CT-score than patients without asthma (mean rank 40 vs. 15.2, p 0.001). ASQ score was significantly higher among allergic nasal polyp patients with asthma compared to patients without asthma (mean rank 40.1 and vs. 14.1, p 0.002). Most allergic nasal polyp with concomitant asthma had eosinophilic-predominate pathological subtypes (81.1%) while all patients without asthma had neutrophilic-predominant pathological subtypes (p 0.003).

Table (2): Comparison of studied variablesbetween allergic nasal polyp with group and allergic nasal poly group without bronchial asthma

| Item | | Allergic nasal poly group | | Stat.test | P-value |
|---|---|---|---|---|---|
| | | With Asthma (n = 37) | Without asthma (n = 23) | | |
| Age /yrs. | Mean ± SD | 40.4± 11.1 | 38.3± 9.9 | t = 0.73 | 0.465 |
| Sex | Male | 30 (81.1%) | 11 (47.8%) | $X^2$ = 7.2 | 0.007* |
| | Female | 7 (18.9%) | 12 (52.2%) | | |
| Smoking | Smokers | 25 (67.6%) | 7 (30.4%) | $X^2$ = 7.8 | 0.005* |
| | Non-smokers | 12 (32.4%) | 16 (69.6%) | | |
| Eosinophil% | Median (IQR) | 4.1 (3.4 - 5.2) | 2.1 (1.8-2.7) | MW = 74 | 0.001* |
| | Mean rank | 40 | 15.2 | | |
| SFAR-score | Median (IQR) | 12 (10.5-13) | 8 (7 – 9) | MW=85.5 | 0.001* |
| | Mean rank | 39.7 | 15.7 | | |
| NOSE-score | Median (IQR) | 13 (12 – 14) | 9 (8 – 10) | MW=54.5 | 0.001* |
| | Mean rank | 40.5 | 14.4 | | |
| Endoscopic sinus-score | Grade 1 | 0 (0%) | 9 (39.1%) | $X^2$ = 26.3 | 0.003* |
| | Grade 2 | 11(29.7%) | 7 (30.4%) | | |
| | Grade 3 | 21 (56.8%) | 1 (4.3%) | | |
| | Grade 4 | 5 (13.5% | 6 (26.1%) | | |
| Lund and Mackey CT-score | Median (IQR) | 19 (17.5-21.5) | 14 (11 – 16) | MW = 74 | 0.002* |
| | Mean rank | 40 | 15.2 | | |
| ASQ-score | Median (IQR) | 12 (11 – 13) | 2 (1 – 4) | MW = 49 | 0.003* |
| | Mean rank | 40.6 | 14.1 | | |
| Pathological subtypes of polyp | Eosinophilic predominant | 30 (81.1%) | 0 (0%) | $X^2$ = 37.3 | 0.001* |
| | Neutrophilic predominant | 7 (18.9%) | 23 (100%) | | |

t: Independent sample T test, $X^2$: Chi-square test, MW: Mann Whitney U test, *: Significant p-value

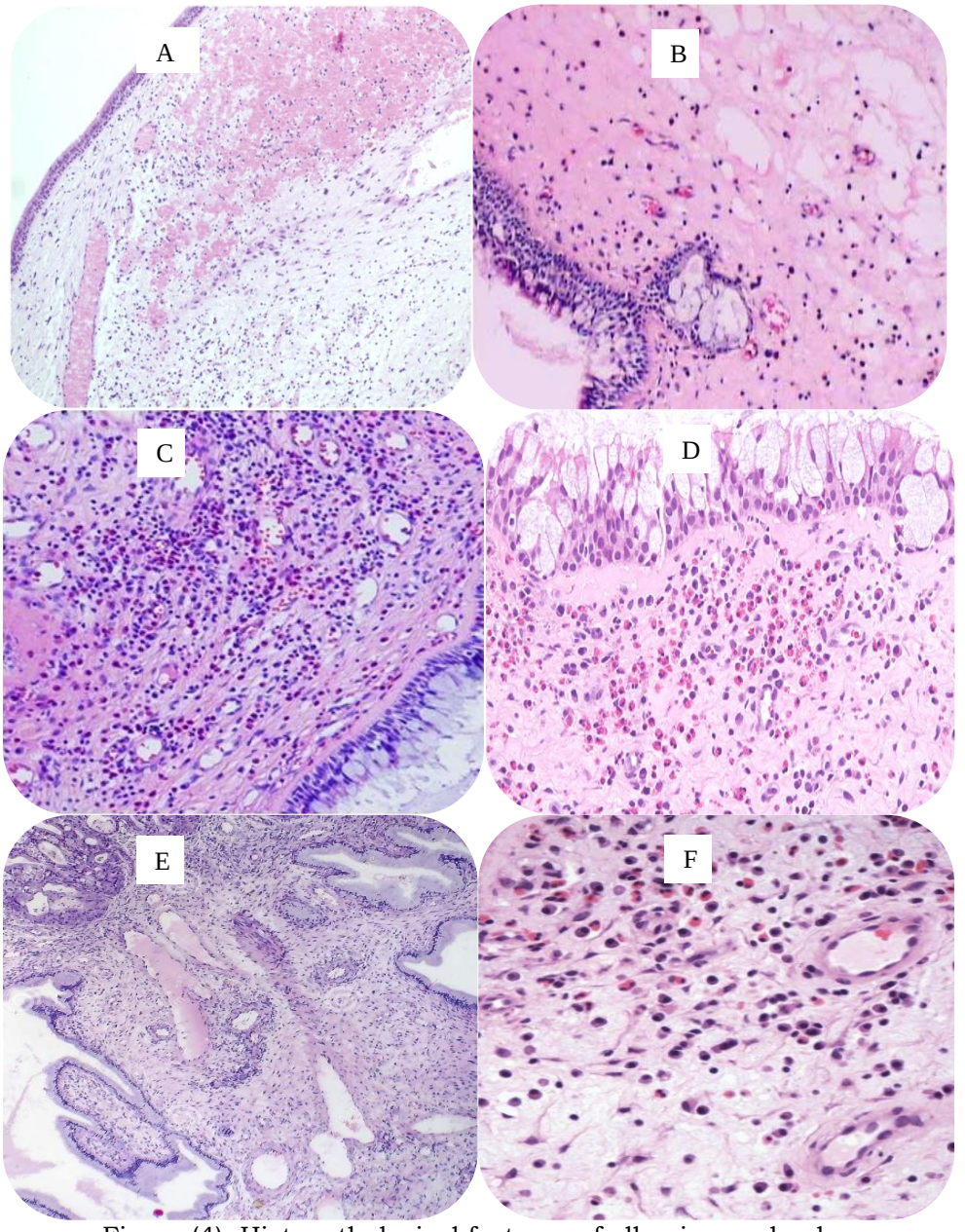


Figure (4): Histopathological features of allergic nasal polyp

Inflammatory nasal polyp lined with respiratory pseudostratified columnar ciliated epithelium with underlying stroma showing marked edema(A), and mixed inflammatory cell infiltrate rich in neutrophils (B). Allergic nasal polyp with dense esinophil-rich inflammatory infiltrate with dilated ectatic vessels and thickened basement membrane (C, D, E) .Secondary hyperplastic changes were noted with mucus gland hyperplasia (F).

Table (3) shows that all spirometric-indices ($FEV_1$/FVC ratio, $FEV_1$%, FVC% and FEF %) were negatively correlated with SAFR-score, ASQ-score, NOSE-score, Lund and Mackey CT-score, blood eosinophil %, and endoscopic-score ($p< 0.05$).

Table (3): Correlation of spirometric-indices with other studied variables in allergic nasal polyp group

| Variables | $FEV_1$/FVC ratio | | $FEV_1$% | | FVC% | | FEF25-75% | |
|---|---|---|---|---|---|---|---|---|
| | r | P | r | p | r | p | r | p |
| SAFR-score | -0.58 | 0.001* | -0.55 | 0.002* | -0.49 | 0.002* | -0.47 | 0.002* |
| ASQ-score | -0.83 | 0.001* | -0.82 | 0.001* | -0.62 | 0.001* | -0.72 | 0.001* |
| NOSE-score | -0.73 | 0.001* | -0.71 | 0.001* | -0.56 | 0.002* | -0.60 | 0.001* |
| Lund and Mackey CT-score | -0.66 | 0.001* | -0.65 | 0.001* | -0.47 | 0.003* | -0.49 | 0.002* |
| Blood eosinophil % | -0.60 | 0.001* | -0.59 | 0.001* | -0.53 | 0.002* | -0.53 | 0.003* |
| Endoscopic-score | -0.41 | 0.003* | -0.38 | 0.003* | -0.36 | 0.004* | -0.31 | 0.014* |

r: Pearson correlation coefficient. *: Significant p-value

Table (4) demonstrates that the most relevant predictive risk factors of asthma in patients with allergic nasal polyp in descending orders were; smoking (OR=4.76 , p 0.006), male sex (OR=4.6, p0.009), higher SAFR-score (OR=0.21, p0.001), increased eosinophils % (OR=0.049, p0.001), and higher Lund and Mackey CT-score (OR=0.54, p 0.001).

Table (4): Multivariate logistic regression analysis for risk factors predictive of bronchial asthma in patients with allergic nasal polyps (n = 60)

| | B | SE | p-value | OR | 95% CL | |
|---|---|---|---|---|---|---|
| Age \ yr. | -0.026 | 0.026 | 0.310 | 0.97 | 0.92 | 1.02 |
| Sex | 1.54 | 0.59 | 0.009* | 4.6 | 1.46 | 14.9 |
| Smoking | 1.56 | 0.57 | 0.006* | 4.76 | 1.5 | 14.6 |
| SAFR-score | - 1.55 | 0.41 | 0.001* | 0.21 | 0.09 | 0.47 |
| NOSE-score | - 16.6 | 2582.9 | 0.995 | 0.0 | --- | --- |
| Blood eosinophil % | - 3.02 | 0.82 | 0.001* | 0.049 | 0.01 | 0.24 |
| Lund and Mackey CT-score | - 0.61 | 0.16 | 0.001* | 0.54 | 0.39 | 0.74 |
| ASQ-score | - 7.08 | 1270 | 0.996 | 0.001 | ---- | ---- |

B: Regression coefficient, SE: Standard error, CL: Confidence interval, *: Significant p-value

Table (5) shows that by using ROC curve the ASQ-score at a cutoff level of >7.5, and AUC=0.94, had 97.3% sensitivity, 95.6% specificity, 95.7% PPV and 97.3% NPV in diagnosis of bronchial asthma in patients with allergic nasal polyp.

Table (5): Diagnostic performance of ASQ for diagnosis of bronchial asthma in patients with allergic nasal polyp

| | Cut off | AUC | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| ASQ-score | > 7.5 | 0.94 | 97.3 % | 95.6 % | 95.7 % | 97.3% |

PPV: positive predictive value, AUC: Area under curve, NPV: negative predictive value, *: Significant p-value

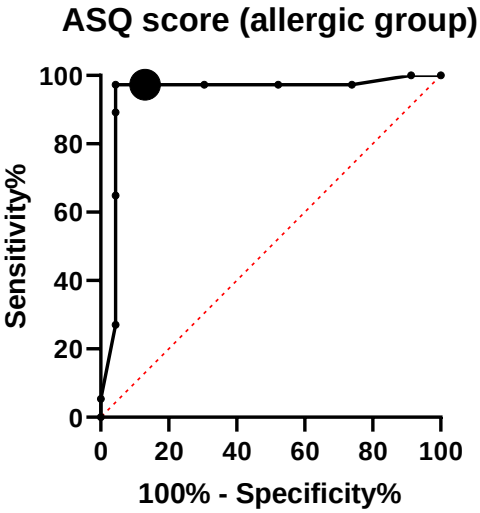


Figure (5): ROC curve of ASQ in diagnosis of bronchial asthma in patients with allergic group

**Discussion**

Allergic rhinitis and asthma are considered as manifestations of one inflammatory process rather than distinct diseases (Bousquet et al, 2018). So early diagnosis and management of asthma in patients with allergic nasal polyp will improve outcome and help in control of both disorders.Recently, patients with CRSwNP without clinically detected lower airway disease were found to have latent lower obstructive changes, even without airway hyperresponsiveness. Nevertheless, the pulmonary function tests (PFT) of patients with CRSwNP is not yet completely understood, and the association between histopathological features in tissue and lower pulmonary disease manifestations remains mostly unclear (Ismail et al., 2022).

Patients with CRSwNP often have coexisting asthma under the concept of “United Airway Disease”. Although clinicians have recognized this difficult-to-treat phenotypefor many years, it remained poorly characterized (Langdon and Mullol ., 2016). As expected the current study revealed that patients with allergic nasal polyps had significantly higher SFAR-score, NOSE-score, endoscopic sinus examination score, peripheral eosinophil% and Lund and Mackey CT-score compared to controls.

The main findings of the current study is that patients with allergic nasal polyps have significant reduction of all spirometric-indices with significant increase of ASQ-score ($p < 0.05$). Accordingly, subclinical asthma was significantly prevalent in patients with nasal polyps than controls (61.7% vs. 10%). Moreover, asthma was significantly more severe in patients with allergic nasal polyp as 16.2 % of them have moderate asthma (p 0.031). Evidence has shown that CRSwNP and asthma share not only a physical link of the affected organs, but also biochemical, histological, and clinical characteristics (Promsopa et al., 2016).

Several theories explain the relationship between upper and lower airways;one is that nasopharyngo-bronchial reflexes is possibly involved in inducing lower airway hyperresponsiveness. Local stimulus by inflammatory mediators might initiate bronchospasm, the suggested mechanism is that local upper respiratory tract inflammatory process may reflected to the lower airways through chemotactic factors and leukocytes that increase cell adhesion receptors (Lee et al., 2014).

Additionally, both have related histological and anatomical structures. Pathological changes of the lower airway maybe stimulated by existence of upper airway inflammation (Ismail et al., 2022).Youssef et al.(2017) draw attention to the role of nasal blockage in occurrence of lung disease with loss of function of the nose for warming, cleaning and humidifying the inspired air and with loss of its defensive mechanisms. Patients with CRSwNP identified as having a type 2 immune response including involvement of IgE, eosinophils, IL-4/IL-13, and IL-5 often have more severe disease with higher rates of polyp recurrence and difficult-to-treat asthma (Laidlaw et al.,2021).

Similarly, Ragab et al. (2004) found involvement of lower airways in 60% of adult patients with chronic allergic rhino-sinusitis refractory to medical treatment: some are manifested as asthma, while others are not manifested (just bronchial hyperresponsiveness). Williamson et al. (2011) found subclinical diminishment of $FEV_1$ and FEF25-75 in CRSwNP. Tanaka et al. (2014) reported that 13% of patients with CRSwNP and 20% of patients with CRSwNP combined with blood eosinophilia had obstructive pulmonary dysfunction ($FEV_1$/FVC \70%) even with the nonexistence of an asthma diagnosis.

Ciprandi et al. (2005) concluded that 53.7% of allergic chronic rhinosinusitis patients had decreased pulmonary function tests. Kariya et al. (2004) reported that latent obstruction of small airways was associated with chronic rhinosinusitis even where they caused no symptoms and had not led to a diagnosis of obstructive airway disease. There was a male predominance in allergic nasal polyp's group with concomitant asthma than group without asthma (p 0.007), and it was a predictive risk factor for asthma in patients with allergic nasal polyps. These findings may represent a sex-specific genetic influence on airway functions.Although the direct effects of sex hormones have not been comprehensively evaluated; the lymphocytes, monocytes, eosinophils, basophils, and mast cells are known to express receptors for sex hormones (Untersmayr et al., 2016).

Additionally, our patients allergic nasal polyp's with concomitant asthma had significantly higher smoking index compared to those without asthma (0.005), and smoking index was a prevalent predictive risk factors for asthma in patients with nasal polyps. Jayes et al. (2016) concluded thatcigarette smoke plays a substantial role in the development of airway inflammatory diseases, including asthma and chronic rhinosinusitis. Cigarette smoking may increase risk of development of asthma among those with allergic nasal polyp and also both may be due to smoking. Moreover, cigarette smoking is associated with poor resolution of respiratory disease symptoms, resistance to treatment, decline in lung function, and development of irreversible airflow obstruction in asthmatics (Hancox et al.,2016).Such results weren't in agreement with Langdon and Mullol (2016) who reported that the prevalence of asthma among CRSwNP more prevalent in adult female.

There was significantly more advanced nasal polypsindices (higher SFAR, NOSE-score, endoscopic-sinus score, and Lund and Mackey CT-score) among studied patients with concomitant asthma.The spirometric-indices were negatively correlated with SAFR, NOSE-score, Lund and Mackey CT score and endoscopic sinus score in patients with allergic nasal polyp andconcomitant asthma. Moreover, the increased SAFR and Lund and Mackey CT-score are significant important risk factors for asthma inpatients with allergic nasal polyps.

These findings indicate that poorer polyps condition adversely influences lower airway function which may be explained by the concept of the united airways that means that upper airway inflammation may influence lower airway inflammation and function and vice versa. Although the underlying mechanisms to explain these associations remain unclear, research conducted by Fasano ., 2010) suggested that the presence of systemic inflammation triggered by both the adaptive and innate immune system is a major driving force in combined airway diseases. Chronic nasal obstruction also augments the upper airway resistance which will compromise the airflow to the lungs.

Mechanical nasal obstruction results in increased resistance to the inspired air which can indirectly influence pulmonary functions as the nose constitutes 50% of total airway resistance, therefore any mechanical obstruction in it can increase the total airways resistance. Zhang et al. (2016) investigated cases where FEF25-75 and $FEV_1$ were diminished and found that reduced pulmonary function had a correlation with CRSwNP status as shown by CT, in the absence of disease affecting the lower respiratory tract. Moreover, (Ismail et al., (2022) and Karuthedath et al. (2014) found that the PFT was improved significantly following endoscopic sinus surgery in patients with chronic allergic rhinosinusitis. Additionally, Karaman et al. (2011) observed significant improvement in all spirometry parameters following septoplasty except $FEV_1$. In this regard we can expect that surgery for nasal polyps could improve lower airways functions which is documented by Siam etal. (2020) as functional endoscopic sinus surgery have a positive effect on the pulmonary function of patients with CRSwNP.

The current study revealed that the blood esinophils% was significantly higher in patients with allergic polyp than controls and in patients with polyp and coexistent asthma than those without asthma. Moreover, patients with coexistent

asthma had predominant-eosinophilic pathological subtype compared to those without asthma. Additionally, the increased blood eosinophils % is a significant risk factor for asthmadevelopment. These findings indicate that eosinophilic inflammation plays an important role in the pathogenesis of both allergic polyp and asthma, and it is one of the key inflammatory mediators for worsening of both upper and lower airway conditions as the main source of chronic inflammatory mediators (Kuruvilla et al., 2019).

The pathophysiology of CRSwNP remains unclear; however, eosinophilic inflammation has been reported to play a critical role in it (Snidvongs et al.,2012). Eosinophils may contribute to nasal polyp formation and growth not only through inflammation but also by exerting their effects on extracellular matrix including stimulation of collagen synthesis (Jankowski 1996). Eosinophilic inflammation orchestrated by allergic sensitization and T helper 2 lymphocytes-mediated immune response is the hallmark of airway inflammation in asthma, but importantly eosinophilic inflammation can occur independent of allergy and the presence of eosinophilic inflammation is neither necessary nor sufficient for the development of asthma (Eltboli and Brightling ., 2013).

On the other hand, asthmatic patients with comorbid CRSwNP have higher levels of lower airway inflammation and worse asthma control than those without CRSwNP, and they have greater sputum eosinophilia and impaired lung function compared to patients without CRSwNP. Histological studies have demonstrated high levels of eosinophils in nasal polyp tissues (Snidvongs et al.,2012), Novelli et al.(2018). Erkan et al 2007, and Giuseppe et al .,2009 studies have shown that regarding the association between CRS and asthma, patients with CRSwNP had more severe asthma phenotype, higher eosinophilic airway inflammation and a lower lung function.There is now evidence that CRSwNP or CRSsNP should be considered two different clinical and pathologic entities with different relationship with lower airways involvement. Jarvis et al.(2012) confirm the close association between CRSwNP and sputum eosinophilia and lower lung function

The significantly higher ASQ-score, the strong negative correlation of spirometric-indices with ASQ, and the very good diagnostic performance of ASQ for asthma in our patients with allergic nasal polyp indicate that ASQ as an inexpensive, simple, noninvasive, validated method andperformed in reasonable short time frame is recommended to be conducted periodically for patients with allergic nasal polyp refractory to medical therapy for early detection of asthma development. The strongest point of the current study is that it highlights the underuse of ASQ and pulmonary function testing for patients with allergic nasal polypwhich may lead to missed diagnosis of concomitant lower airway diseases.

**Conclusions**

Asthma is common in patients with allergic nasal polyp refractory to medical therapy,therefore, allergic nasal polyp can be considered as one of the strongest risk factors for asthma development especially in smokers, males, with higher SAFR-score, higher eosinophils %, and higher CT-score. As ASQ had very good diagnostic performance for asthma in our patients with allergic nasal polyp, so we recommend annual screening of patients with allergic nasal polyp by ASQ, to be

followed by spirometry for patients with positive screening test for confirmation of diagnosis and assessment of the asthma severity for early initiation ofantiasthma treatment which could improve outcome of both disorders.

**References**


Al-Digheari A, Mahboub B, Tarraf H, et al.. The clinical burden of allergic rhinitis in five Middle Eastern countries: results of the SNAPSHOT program. Allergy Asthma Clin Immunol. 2018 Nov 19;14:63.

Alharethy S, Wedami MA, Syouri F, et al. Validation of the Arabic version of the score for allergic rhinitis tool. Ann Saudi Med. 2017 Sep-Oct;37(5):357-361.

Bousquet J, Devillier P, Anto JM, et al. Daily allergic multimorbidity in rhinitis using mobile technology: A novel concept of the MASK study. Allergy. 2018 Aug;73(8):1622-1631.

Bousquet J, Schünemann HJ, Samolinski B, et al. World Health Organization Collaborating Center for Asthma and Rhinitis. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol. 2012 Nov;130(5):1049-62.

Ciprandi G, Cirillo I, Vizzaccaro A, et al. Early bronchial airflow impairment in patients with persistent allergic rhinitis and bronchial hyperreactivity. Respir Med.99(12):1606-12, 2005

Clark DW, Del Signore AG, Raithatha R, et al. Nasal airway obstruction: Prevalence and anatomic contributors. Ear Nose Throat J. 2018 Jun;97(6):173-176.

Eltboli O, Brightling CE. Eosinophils as diagnostic tools in chronic lung disease. Expert Rev Respir Med. 2013 Feb;7(1):33-42.

Erkan C, Mehmet G, Imran S. Nasal polyps and the severity of asthma. Respirology (Carlton, Vic.). 2007;12. 272-6.

Fasano MB. Combined airways: impact of upper airway on lower airway. Curr Opin Otolaryngol Head Neck Surg. 2010 Feb;18(1):15-20.

Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012 Mar;50(1):1-12.

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Giuseppe G, Giovanni R, Iuliana B,et al. Determinants of Exhaled Nitric Oxide in Chronic Rhinosinusitis. Chest. 2009;137. .

Hancox RJ, Gray AR, Poulton R, et al. The effect of cigarette smoking on lung function in young adults with asthma. Am J Respir Crit Care Med 2016;194:276–84

Ismail HM, Mekhemar SM , Mostafa SY, et al. Impacts of sinonasal polyposis on pulmonary function pre and post function endoscopic surgery. JRAM 2022; 3(1):45-52.

Jankowski R. Eosinophils in the pathophysiology of nasal polyposis. Acta Otolaryngol. 1996 Mar;116(2):160-3. doi: 10.3109/00016489609137813. PMID: 8725504.

Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67:91–8

Jayes L, Haslam PL, Gratziou CG, et al. SmokeHaz: systematic reviews and meta-analyses of the effects of smoking on respiratory health. Chest 2016;150:164–79. S0012-3692(16)48547-8

Karaman M, Tek A, Tuncel A, et al. Evaluation of patients with septal deviation using respiratory function tests before and after septoplasty. Kulak Burun Bogaz Bas Boyun Cerrahi Derg. 2011;19(1):1-5

Kariya S, Okano M, Oto T, et al. Pulmonary function in patients with chronic rhinosinusitis and allergic rhinitis. J Laryngol Otol. 128:255-62, 2014.

Karuthedath S, Singh I, Chadha S. Impact of Functional Endoscopic Sinus Surgery on the Pulmonary Function of Patients with Chronic Rhinosinusitis: A Prospective Study. Indian J Otolaryngol Head Neck Surg. 2014 Dec;66(4):441-8

Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol. 2019 Apr;56(2):219-233.

Laidlaw TM, Mullol J, Woessner KM, et al. Chronic Rhinosinusitis with Nasal Polyps and Asthma. J Allergy Clin Immunol Pract. 2021 Mar;9(3):1133-1141.

Langdon C, Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. J Asthma Allergy. 2016 Mar 14;9:45-53.

Lee S, Yoon S, Song W, et al. Influence of chronic sinusitis and nasal polyp on the lower airway of subjects without lower airway diseases. Allergy Asthma Immunol Res. 2014; 6(4):310-315.

Lund Valerie and Mackay I. Staging in Rhinosinusitis. Rhinology.1994; 31. 183-4.

Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc. 2011;86(5):427–443. doi: 10.4065/mcp.2010.0392.

Miller MR, Hankinson J, Brusasco V,et al. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319-38.

Novelli F, Bacci E, Latorre M, et al. Comorbidities are associated with different features of severe asthma. Clin Mol Allergy. 2018 Dec 3;16:25.

Promsopa C, Kansara S, Citardi MJ, et al. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. Int Forum Allergy Rhinol. 2016 Apr;6(4):373-7.

Ragab A, Clement P, Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. Am J Rhinol. 2004;18:16-21

Shin B , Cole S.L, Park S-J ,et al. A New Symptom Based Questionnaire for Predicting Asthma. Journal of investigational allergology & clinical immunology : official organ of the International Association of Asthmology (INTERASMA) and Sociedad Latinoamericana de Alergia e Inmunología.2010; 20. 27-34.

Siam E , Al-Morsy M, abouzaid M. Impact of functional endoscopic sinus surgery for cases with nasal polypi on pulmonary function tests. *Al-Azhar International Medical Journal*, 2020; 1(2): 173-178.

Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. Int Forum Allergy Rhinol. 2012 Sep-Oct;2(5):376-85.

Tanaka S, Hirota T, Kamijo A, et al. Lung Functions of Japanese Patients with Chronic Rhinosinusitis Who Underwent Endoscopic Sinus Surgery. Allergology International. 63:27-35, 2014

Untersmayr E, Jensen AN ,Walch K. Sex hormone allergy: clinical aspects, causes and therapeutic strategies: update and secondary publication. World Allergy Organ J. 2017; 10: 45.

Vennilavan RN, Spalgais S, Kumar R. Asthma phenotype: Clinical, physiological, and biochemical profiles of North Indian patients. Lung India. 2022 Mar-Apr;39(2):121-128.

Williamson PA, Vaidyanathan S, Clearie K, et al. Airway dysfunction in nasal polyposis: a spectrum of asthmatic disease? Clin Exp Allergy. 41(10):1379-85, 2011.

Youssef AM, Awad OGA, Taha M. Pulmonary Function of Patients with Chronic Rhinosinusitis and the Impact of Endoscopic Sinus Surgery. OTO Open. 2017 Oct 27;1(4):2473974X17738759.

Zhang L, Zhang L, Zhang CH, et al. The Lung Function Impairment in Non-Atopic Patients With Chronic Rhinosinusitis and Its Correlation Analysis. *Clin Exp Otorhinolaryngol.*, 2016; 9(4): 339–45.