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Determining the Severity of Symptoms Among Patients with Eosinophilic Chronic Rhinosinusitis with Nasal Polyposis Versus Non - Eosinophilic Chronic Rhinosinusitis with Nasal Polyposis at the Veterans Memorial Medical Center

ABSTRACT

Objective: To compare the severity of symptoms of patients diagnosed with Eosinophilic Chronic Rhinosinusitis with Nasal Polyposis (eCRSwNP) versus Non - Eosinophilic Chronic Rhinosinusitis with Nasal Polyposis (non-eCRSwNP) using the Filipino Sinonasal Outcome Test (Filipino SNOT 22) and determine the most common symptoms experienced by patients with eCRSwNP versus non-eCRSwNP.

Methods:

Design: Cross-Sectional Study

Setting: Tertiary Government Training Hospital

Participants: A total of 68 patients diagnosed with Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) from November 7, 2018 to August 31, 2022 were included in the study.

Results: Of the 68 patients included in the study, 33 (48.5%) had non-eCRSwNP while 35 (51.5%) had eCRSwNP. The age of the patients with non-eCRSwNP group was 50.6 + 18.45 and those with eCRSwNP was 52.9 + 16.6 years old. Non-eCRSwNP patients had a lower mean Filipino SNOT-22 score of 39.7 ± 16.1 compared with eCRSwNP with a score of 62.7± 13.5. The non-eCRSwNP patients had symptom severity classified as mild in 2 (6.1%), moderate in 25 (75.8%) and severe in 6 (18.2%) based on Filipino SNOT-22. Among the eCRSwNP group, majority of the patients, 29 (82.9%) were classified as severe, 6 (17.1%) as moderate, and none with mild severity. Using the Filipino SNOT 22, the most common symptoms of patients with eCRSwNP were item 2 (*baradong ilong;* nasal blockage) at 28.6%, then item 7 (*malapot na sipon;* thick nasal discharge) at 25.7%, Item 8 (*pagbabara ng tenga*; ear fullness) and item 12 (*pagkawala/ pagkabawas ng panlasa/ pang-amoy;* decreased sense of smell/taste) were tied at 14.3%, item 13 (*hirap sa pagtulog;* difficulty falling asleep) at 25.7%, and item 17 (*pagkapagod;* fatigue during the day) at 31.4% while patients with no-eCRSwNP were noted with item 2 (*baradong ilong;* nasal blockage) at 48.5%, followed by item 4 (*hindi tumitigil na pagtulo ng sipon;* runny nose) at 21.2%, item 11 (*pananakit ng mukha;* facial pain) at 33.3%, Item 7 (*malapot na sipon;* thick nasal discharge) at 18.2%, and item 20 (*pagiging irritable/pagkainis;* irritability) at 21.2%.

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Conclusion: Our present study suggests that the higher the SNOT-22 score, the more likely it is to be eosinophilic chronic rhinosinusitis. Although nasal blockage was the most common symptom found in both patients with eCRSwNP and non-eCRSwNP, patients with thick nasal discharge, decreased sense of smell/taste and ear fullness were more likely to be suffering from eCRSwNP, while patients with runny nose, facial pain and thick nasal discharge were more likely to have non-eCRSwNP.

Keywords: *chronic rhinosinusitis; eosinophilic chronic rhinosinusitis; non-eosinophilic chronic rhinosinusitis; chronic rhinosinusitis with nasal polyposis; nasal polyposis; sinusitis; endoscopic surgical procedure; snot-22; nasal congestion; nasal blockage*

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases but little is understood about its pathogenesis.[1] It is primarily an inflammatory disorder due to multiple etiologic factors and is defined as inflammation of the nasal cavity and paranasal sinuses and/ or the underlying bone that has been present for at least 12 weeks.[1,2] There is increasing prevalence of chronic rhinosinusitis. In Europe, the prevalence of CRS is confirmed at 10.9%.[2] Moreover, the diagnosis of CRS was made 2.6 million times in 2002 in Germany according to the German Guideline of Rhinosinusitis.[2] In Korea, there is an increase of prevalence in 2008 to 7.12%.[3] There is increasing evidence that the recalcitrance and chronicity of this disease is due to a deranged host immune response against environmental agents.[4] In 2011, Nakayama *et al.* introduced a new classification of chronic rhinosinusitis where they concluded that the presence of mucosal eosinophilia is a more important factor than nasal polyps for classifying CRS in terms of the surgical outcome.[5] Subsequently in 2015, Tokunaga *et al.* introduced a novel scoring system and algorithm for classifying chronic rhinosinusitis called the JESREC study. This study concluded that eosinophilic chronic rhinosinusitis (eCRS) significantly correlated with prognosis and refractoriness of the disease.[6]

Symptom severity is one of the important aspects of chronic rhinosinusitis with nasal polyposis (CRSwNP). Symptoms of chronic rhinosinusitis can be nasal blockage/ obstruction/ congestion, nasal discharge (anterior/posterior nasal drip), facial pain/pressure, reduction or loss of smell. The Sinonasal Outcome Test (SNOT) 22 is a self-administered questionnaire designed to determine the severity of symptoms of an individual with chronic rhinosinusitis. A score of 8-20 is mild, >20-50 is moderate and >50 is severe. The 22-question survey has been modified by the National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis by the Royal College of Surgeons of England and measures the physical impairments, functional limitations, disability, and societal limitations caused by chronic rhinosinusitis.[7] It has been used by various studies and has been translated and validated into the Filipino Sinonasal Outcome Test.[8] SNOT 22 is mainly used in this study since this tool is a disease specific health related quality of life questionnaire used to measure the outcome of sinonasal disorders specially chronic rhinosinusitis and nasal polyposis.

The aim of this study is to compare the severity of symptoms of patients diagnosed with eosinophilic chronic rhinosinusitis with nasal polyposis (eCRSwNP) versus non - eosinophilic chronic rhinosinusitis with nasal polyposis (non-eCRSwNP) and determine the most common symptom presented by patients using the Filipino Sinonasal Outcome Test (Filipino SNOT 22). This paper will serve as a baseline research in our institution that may guide the clinician in predicting the classification of CRSwNP based on symptom severity.

METHODS

With approval of the Veterans Memorial Medical Center (VMMC) Institutional Review Board, this prospective cross- sectional study recruited patients with CRSwNP who underwent endoscopic sinus surgery (ESS) at the VMMC. Purposive sampling was used to select patients diagnosed with CRSwNP who underwent ESS with removal of nasal polyps.

Excluded were patients diagnosed with sinonasal papilloma and intranasal/ paranasal sinus malignancies. The diagnosis of CRSwNP was made according to the Clinical Practice Guidelines of the Philippine Society of Otolaryngology - Head & Neck Surgery[1] and was based on the presence of two or more of the following symptoms, one of which should either be: (a) nasal blockage/ obstruction/ congestion; (b) nasal discharge (anterior/posterior nasal drip); (c) facial pain/pressure; and (d) reduction or loss of smell. These symptoms must have been present for a duration of 12 weeks or more. In addition, diagnosis was based on the presence of the following objective evidence of inflammatory disease: (a) mucopurulent discharge primarily from the middle meatus; (b) nasal polyps; (c) edema/ mucosal obstruction primarily in the middle meatus; and (d) radiographic imaging showing mucosal changes within the ostiomeatal complex and/or sinuses that has been present for at least 12 weeks.

Patients who were clinically diagnosed with CRSwNP who signed the consent form were included in the study. The Filipino Sinonasal Outcome Test 22 (SNOT 22) was administered to patients who were asked to answer the questionnaire to determine symptom severity (8-20 as mild, >20-50 moderate and >50 severe). The patients underwent routine ESS.

Nasal polyps removed during the surgery were immediately sent to the Department of Pathology for histological examination. The sections were stained with hematoxylin-eosin and the number of eosinophils and inflammatory cells in the specimen were quantified under high-power field (HPF × 400) where they were the densest cellular infiltrate beneath the epithelial surface. Histological examinations were performed by a

senior pathology resident and board certified pathologist unaware of the clinical data, and the mean number of eosinophils were calculated by same pathologists using the JESREC classification. According to the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) study,[6] the number of eosinophils equal or higher than 70/HPF were defined as eosinophilic chronic rhinosinusitis with nasal polyposis.

Data were collected using a data collection form and encoded in Microsoft® Excel 2019 MSO Version 2409 Build 16.0.18025.20030 64-bit (Microsoft Corp., Redmond WA, USA) and analyzed using SPSS for windows version 26 (IBM Corp., Armonk, NY, USA). Age and SNOT-22 score were reported using median and interquartile range (IQR) since these variables followed non-normal distribution based on Shapiro-Wilk test ($W = .876$, $p < .001$ for age; $W = .939$, $p = .002$ for SNOT-22 score). Categorical variables were summarized using frequency and percentage. Demographic characteristics and severity profile based on SNOT-22 score of non-eosinophilic and eosinophilic groups were compared using Mann-Whitney U-test for numerical variables such as age and SNOT-22 score and Fisher-exact test for categorical variables such as symptom severity. All tests were performed at 5% significance level.

RESULTS

A total of 68 patients diagnosed with chronic rhinosinusitis with nasal polyposis (CRSwNP) who underwent ESS with polypectomy from November 7, 2018 to August 31, 2022 were included in the study. Based on histological type, the prevalence of non-eosinophilic chronic rhinosinusitis with nasal polyposis (non-eCRSwNP) was 33 (48.5%), while the remaining 35 cases were eosinophilic chronic rhinosinusitis with nasal polyposis (eCRSwNP) with a prevalence rate of 51.5%. It was observed that patients in the non-eCRSwNP group had a median age of 55 (IQR: 46 to 63 years). On the other hand, those with eCRSwNP had a median age of 57 years (IQR: 46 to 64 years). Comparison using Mann-Whitney U-test showed that there was no significant difference in age between Non-eCRSwNP and eCRSwNP groups ($U = 546$, $p = .694$). It was also observed that the proportion of males among non-eCRSwNP patients (85%) was higher compared to eCRSwNP patients (66%). However, Fischer-exact test showed that there was no significant association between sex and eCRSwNP ($p = .094$).

The overall Filipino SNOT-22 score had a median of 51.5 (IQR: 34.5 to 69.5). The non-eCRSwNP group had a lower median Filipino SNOT-22 score of 35 (IQR: 29 to 45) compared with the eCRSwNP with a median score of 69 (IQR: 53 to 73). Mann-Whitney U-test revealed a statistically significant difference of SNOT-22 scores between groups ($U = 171$, $p < .001$). The Filipino SNOT-22 scores were further stratified into mild (8-20), moderate (>20-50), and severe (>50). Among those with non-eCRSwNP, 6.1% were classified as mild, 75.8% as moderate and 18.2% as severe. On the other hand, among those with eCRSwNP, majority of the scores were classified as severe at 94.3% of total patients while the remaining 17.1% were classified to have moderate symptoms. In addition, there is a significant association between the severity of symptoms of non-eCRSwNP vs eCRSwNP based on Fisher-exact test ($p < .001$).

The most common symptom experienced among all patients was item 2 (*baradong ilong;* nasal blockage) at 38.2%, followed by item 7 (*malapot na sipon;* thick nasal discharge) at 20.6%, item 12 (*pagkawala/ pagkabawas ng panlasa/ pang-amoy;* decreased sense of smell/taste) at 23.5%, 13 (*hirap sa pagtulog;* difficulty falling asleep) at 19.1%, and lastly item 17 (*pagkapagod;* fatigue during the day) at 20.6 %. For those with non-eCRSwNP, the most bothersome symptom was item 2 (*baradong ilong;* nasal blockage) at 48.5%, followed by item 4 (*hindi tumitigil na pagtulo ng sipon;* runny nose) at 21.2%, item 11 (*pananakit ng mukha;* facial pain) at 33.3%, Item 7 (*malapot na sipon;* thick nasal discharge) at 18.2%, and item 20 (*pagiging irritable/ pagkainis;* irritability) at 21.2%. For patients classified as eCRSwNP, the most bothersome symptom was item 2 (*baradong ilong;* nasal blockage) at 28.6%, then item 7 (*malapot na sipon;*thick nasal discharge) at 25.7%, Item 8 (*pagbabara ng tenga;* ear fullness) and item 12 (*pagkawala/ pagkabawas ng panlasa/ pang-amoy;* decreased sense of smell/taste) were tied at 14.3%, item 13 (*hirap sa pagtulog;* difficulty falling asleep) at 25.7%, and item 17 (*pagkapagod;* fatigue during the day) at 31.4%.

DISCUSSION

Our study showed that there is a statistically significant association between the severity of symptoms of patients with non-eCRSwNP and eCRSwNP. This suggests that persons with more severe SNOT-22 scores are more likely suffering from eCRSwNP. A study by Lal *et al.* published in 2018 reported that tissue eosinophilia was highest in those with the highest SNOT-22 scores.[9] This is further supported by a more recent study by Gallo *et al.* where a cluster of subjects with the highest total preoperative SNOT-22 scores had the highest tissue eosinophilia compared to the other symptomatic groups and a more frequent diagnosis of asthma, suggesting that a high burden of inflammation correlates with worse symptomatology.[10] Patients with eCRSwNP show a strong possibility of overlapping mechanisms for eosinophilia and have a poor response to medical and surgical management. This may mean that patients with CRSwNP who have a severe SNOT-22 score may be suspected as a case of eCRSwNP. Therefore, these patients may be advised of a poorer response to both medical and surgical management, and a possible increased risk of recurrence after surgery. In 2017, a study by Sun *et al.* reported that patients with eCRSwNP demonstrated a longer duration of symptoms and higher symptom score compared to non-eCRSwNP.[11] In other studies, those with eCRSwNP commonly have more severe disease and higher symptom scores compared to those with non-eCRSwNP.[12-14]

In our present study, the most common symptom found in both eCRSwNP and non-eCRSwNP was *baradong ilong* (nasal blockage), however, it was also noted that patients classified as eCRSwNP had *malapot na sipon* (thick nasal discharge), *pagbabara ng tenga* (ear fullness) and *pagkawala/ pagkabawas ng panlasa/ pang-amoy* (decreased sense of smell and taste). The thickness of the nasal discharge maybe due to the eosinophilic infiltration in the ethmoidal mucosa.[12] A study by Yoshimura *et al.* shows that there is high prevalence of olfactory dysfunction in eCRSwNP which was said to occur as one of the predominant early symptoms of eCRSwNP compared to non-eCRSwNP.[15] Moreover, eCRSwNP tends to be associated with olfactory cleft opacification that may lead to olfactory dysfunction.[12] In non-eCRSwNP, patients were noted to have *hindi tumitigil na pagtulo ng sipon* (runny nose), *pananakit ng mukha* (facial pain) and *malapot na sipon* (thick nasal discharge). Reports showed that such cases of non eCRSwNP may have different clinical features and may be more of a neutrophil dominant as a consequence of chronic inflammation.[14-16] These studies show little information regarding non-eCRSwNP based on symptoms, and it may be difficult to discern based on symptoms whether it is eCRSwNP and non-eCRSwNP due to their shared symptoms.[15,16]

Our present study found that there was male preponderance among all patients with CRSwNP but this was the same for both non-eCRSwNP and eCRSwNP and statistical analysis did not reveal a statistically significant difference between the two groups. Conversely, Stevens *et al.* in 2016 found that eCRSwNP was commonly seen among males and non-eCRSwNP commonly observed among female patients but no specific genetic nor environmental factors were linked to the development of this disorder.[17]

In our present study, the majority of patients with non-eCRSwNP had a SNOT-22 score of moderate with a frequency of 75.8%. On the other hand, most of the patients with eCRSwNP had a severe SNOT-22 score with a frequency of 82.9%. In 2017, a study by Sun *et al.* reported that patients with eCRSwNP demonstrated a longer duration of symptoms and higher symptom scores compared to non-eCRSwNP.[11] In other studies, those with eCRSwNP commonly have more severe disease and higher symptom scores compared to those with non-eCRSwNP.[12-14]

Our present study has several limitations. It was conducted in a single institution with a limited sample size and data obtained may be inadequate for generalizability. We recommend performing a multi-center study with a larger sample size. Moreover, the history of atopy and asthma which can be used in differentiating between the two disease entities may be included among the data to be obtained. Also, the use of preoperative antihistamines and steroids should be included in the data because it will affect the findings for tissue eosinophilia and the severity of symptoms. Lastly, further investigation of blood eosinophil levels, CT Scan and nasal endoscopic findings among patients with CRSwNP is an area of interest that may determine if these may be used in predicting eCRSwNP and non-eCRSwNP.

In conclusion, we found a statistically significant difference between the scores of patients categorized as eCRSwNP and non-eCRSwNP using SNOT-22, suggesting that the higher the SNOT-22 score, the more likely it is to be eosinophilic chronic rhinosinusitis. Although nasal blockage was the most common symptom found in both patients with eCRSwNP and non-eCRSwNP, patients with thick nasal discharge, decreased sense of smell/taste and ear fullness were more likely to be suffering from eCRSwNP, while patients with runny nose, facial pain and thick nasal discharge were more likely to have non-eCRSwNP.

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