Endotype Conformity with Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) Score in Chronic Rhinosinusitis

Original Article

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ABSTRACT

Introduction: Chronic rhinosinusitis (CRS) is one of the most prevalent disease entities in ORL-HNS field. Management strategy of CRS remains challenging among otorhinolaryngologist. Currently, CRS was known as a heterogeneous disease with various endotypes and phenotypes. By identifying endotypes, comprehensive management strategy in CRS was expected. The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score was a categorical score developed from Japan to diagnose eosinophilic chronic rhinosinusitis (eCRS) and non-eosinophilic chronic rhinosinusitis (non-eCRS). The assessment of JESREC score was expected to have conformity with CRS endotypes so that it can be used as future efficient diagnostic modality.

Objective: This study aims to determine conformity and accuracy of endotype with JESREC score.

Patients and Methods: An analytic study with a cross-sectional design involving 33 samples of primary CRS. Biomarker for specific endotypes measured by ELISA.

Results: Statistical analysis with Mc. Nemar showed no difference/ a conformity between JESREC score and CRS endotypes ($p>0.05$) with sensitivity 61,5% and specificity 90%.

Conclusion: JESREC score is considered a screening modality for CRS endotype.

Key Words: Chronic rhinosinusitis, endotype, JESREC, phenotype.

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INTRODUCTION

Chronic rhinosinusitis remains a social economic burden in Indonesia, and was ranked 25 of the 50 most common disease in Indonesia.[1,2,3] In Saiful Anwar Public Hospital, Malang CRS cases had reached 29% of all outpatient setting and were the most prevalent outpatient cases during 2021.[4,5] According to European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) CRS was subdivided as primary and secondary based on the anatomical site involvement. Host, agent, and environmental factors interact each other to produce CRS endotypes and phenotypes so recently it is known that there were 3 types of endotypes in CRS. Each endotype produces key cytokines that play an important role in inflammatory process of CRS, type 1 produces interferon gamma (IFN-γ) and interleukin 12 (IL-12), whereas type 2 produce IL-4, IL-5, and IL-13, and type 3 produces IL-17A dan IL-22.[6,7,8] By understanding the underlying endotype in each CRS cases, clinician was expected to provide better treatment strategy in CRS.

Biomolecular examination on sinonasal tissue is needed to determine CRS endotype, and it was considered as scarce and high-cost diagnostic method. Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study (JESREC) Score was a categorical score developed in Japan to determine CRS endotype based on four clinical parameters. The JESREC scoring system is considered a more effective, efficient, and non-invasive method for diagnosing endotype in CRS compared to biomolecular examination from sinonasal tissue biopsies. Therefore, this study aims to determine the conformity of endotype and JESREC score in CRS cases.

PATIENTS AND METHODS:

This was an observational study using a cross sectional design carried on 33 adult subjects with primary CRS based on EPOS 2020 criteria and 8 control subjects with chronic sinonasal diseases that not met CRS criteria at ENT clinic Dr. Saiful Anwar Public Hospital, Malang from December 2021 – October 2022. The study population

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were all patients with primary CRS who met the inclusion criteria, which were adult patients aged 18 years or over in accordance to the law of the Republic of Indonesia who met diagnostic criteria for primary CRS. As for control subjects, inclusion criteria were adult patients with chronic nasal complaints that do not meet the diagnostic criteria for CRS based on EPOS 2020 and require surgery on the nose, such as septal deviation and turbinate hypertrophy. Patients who had undergone sinus surgery prior to sampling, had taken antibiotics and systemic or topical corticosteroid 4 weeks prior to sampling, and patient with primary CRS that involved posterior sinuses group, were excluded from the study.

This study was approved by Saiful Anwar Public Hospital ethical committee (400/066/K.3/102.7/2022). Non contrast computed tomography scan (CT-scan) focusing on paranasal sinuses, Lund-Mackay score (LMS) ratio on ethmoid and maxillary sinuses (E/M), nasoendoscopy, and serum eosinophil count were obtained from all CRS subjects to determine each JESREC score. All subjects with primary CRS and control subjects who met the inclusion criteria undergone uncinectomy procedure under general anesthesia. The uncinate process tissues were examined using enzyme-linked immunosorbent assay (ELISA) FineTest kits specific for four biomarkers represented each endotype, IFN-γ for type 1, eosinophil cationic protein (ECP) and Charcot-Leyden crystal (CLC) for type 2, and IL-17A for type 3, with microplate reader ZENIX-320 in Biomedic Central Laboratory of Brawijaya University. Determination of samples endotype was based on its biomarker level compared to controls, where it is said to be positive for a specific endotype if the biomarker level reached more than 90th percentile from control biomarker level.

The conformity between endotype and the JESREC score was analyzed using Mc.Nemar test with 95% confidence interval (CI) and *p-value = 0.05* and considered statistically significant with a $p < 0.05$. Statictical Analysis was performed using Statistical Package of Social Science (SPSS) 26 for Mac software.

RESULTS:

A total of 33 subjects with primary CRS and 8 subjects as control (5 septal deviations and 3 inferior turbinate hypertrophies) was included in this study with age ranged from 18 – 68 years. There were 12 males and 22 females included in primary CRS subjects. Nasal blockage was the main chief complaint in this study, and none of the subjects experienced olfactory dysfunctions. A total of 22 subjects (66.7%) experienced bilateral sinus sites involvement based on paranasal sinus CT-scan, nasal polyp was seen in 16 subjects (48.5%) based on nasoendoscopy examination. As for LMS ratio on ethmoid and maxillary sinuses (E/M ratio), a total of 28 subjects (84.8%) were found to have E/M ratio > 1. On this study, we found 18 subjects (54.5%) have peripheral eosinophil serum percentage less than 2%.

From the ELISA examination, we found that ECP levels in 33 samples of uncinate process tissues ranged from 83.81 – 571.75 pg/mL, CLC protein levels ranged from 0.14 – 1.85 ng/mL, IFN-γ protein levels ranged from 14.52 – 43.49 pg/mL, while IL-17A protein ranged from 20.60 – 187.17 pg/mL. As for control subjects, ELISA examination showed 90th percentile level of 380.74 pg/mL for ECP, 0.68 ng/mL for CLC, 19.29 pg/mL for IFN-γ, and 48.46 pg/mL for IL-17A. A sample is said to have type 1 or type 3 endotype when IFN-γ or IL-17A level exceeds the 90th percentile control level, while it is said to have type 2 inflammation when ECP and/or CLC levels were higher than the 90th percentile control level. A sample can also have a mixed endotype when the biomarkers were higher than the 90th percentile control in two or more biomarkers that represent each cytokine endotype. This interpretation was based on former study conducted by Stevens *et al*. Based on this interpretation, we found that 30 samples (90.9%) samples had single endotype, while 3 samples (9.09%) had mixed endotype. It was found that 10 samples (30.3%) were type 1 endotype, 13 samples (39.39%) were type 2, and 7 samples (21.21%) were type 3. A total of 3 samples with mixed endotype consisted of : mixed type 2 and type 3 for 1 sample (3.03%), and a mixed type 1, 2 and 3 for 2 samples (6.06%). All samples with mixed endotype, were found to have type 2 endotype component, so that in order to carry out statistics and crosstabulation tests, a calculation was made of the percentage deviation between each biomarker and the level of 90th percentile control. Based on this calculation, the 3 mixed endotype samples were found to have highest percentage increase In IL-17A, so they were classified as type 3/ non-type 2 endotype. Thus, there were 2 groups endotypes, namely type 2 and non-type 2 inflammation with respective percentages of 39.39% and 60.61% (Figure 1). Demographic and clinical characteristics of the subjects were presented in (Table 1).

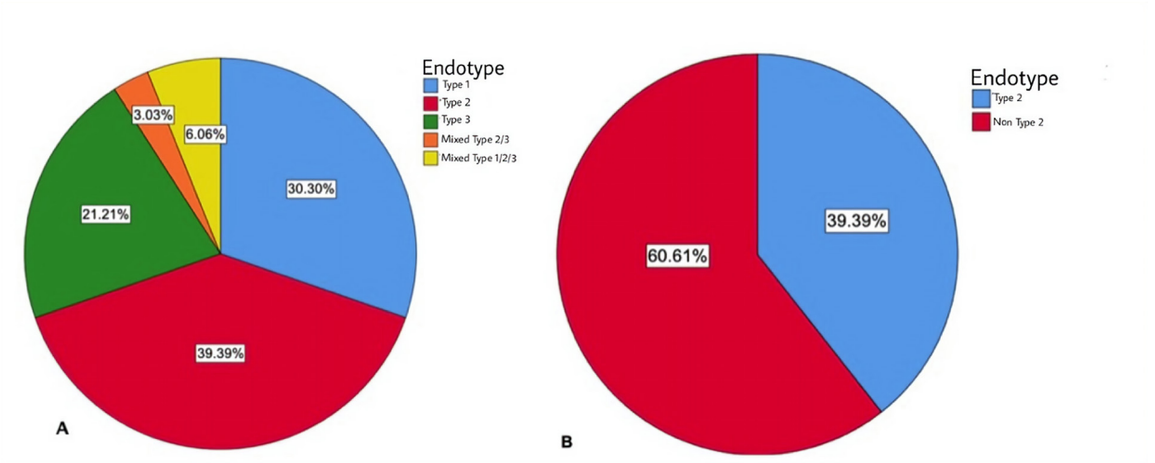

Fig. 1: Endotype group classification found in this study.

JESREC score was calculated on each subjects, a total of 10 subjects (30.3%) have JESREC score > 11 which suggested a possibility of eCRS or type 2 endotype, while 22 subjects (69.7%) have JESREC score < 10 which suggest a non-type 2 endotype. A crosstabulation as seen in (Table 2) was made, Mc. Nemar test shown *p value 0.45 (> 0.05)* which showed no significance/ difference between endotype examination with ELISA as reference standard and JESREC score as index. JESREC score accuracy in diagnosing endotype were 78.8% with 61.5% sensitivity and 90% specificity.

Table 1: Demographic, Clinical Characteristic and Endotype of Patients with Primary CRS

	All subjects (N = 33)	Endotype		
		Type 2 (N = 13)	Non-type 2 (N = 20)	*p*
Sex				
Male	12 (36,4%)	3 (23,1%)	9 (45%)	*0,27*[a]
Female	21 (63,6%)	10 (76,9%)	11 (55%)	
Age (years)				
mean SD	38,4 15,3	33,1 14,1	39,6 17,9	*0,42*[b]
median (min-maks)	32 (18 – 68)	28 (18 – 54)	31,5 (22 - 68)	
Chief complaint				
Blockage	18 (54,5%)	7 (53,8%)	11 (55%)	
Rhinorea	8 (24,3%)	4 (30,8%)	4 (20%)	
Olfactory dysfunction	0 (0%)	0 (0%)	0 (0%)	*0,88*[c]
Facial pain	2 (6%)	0 (0%)	2 (10%)	
Headache	4 (12,1%)	2 (15,4%)	2 (10%)	
Orbita oedema	1 (3,1%)	0 (0%)	1 (5%)	
Paranasal sinus involvement				
Unilateral	11 (33,3%)	2 (15,4%)	9 (45%)	*0,13*[a]
Bilateral	22 (66,7%)	11 (84,6%)	11 (55%)	
Nasal polyp				
Present	17 (51,5%)	10 (76,9%)	7 (35%)	*0,01*[d]
Absent	16 (48,5%)	3 (23,1%)	13 (65%)	
LMS ratio on CT-scan				
Ethmoid < Maxillary (E/M < 1)	5 (15,2%)	1 (7,7%)	4 (20%)	*0,62*[a]
Ethmoid ≥ Maxillary (E/M ≥ 1)	28 (84,8%)	12 (92,3%)	16 (80%)	
Serum Eosinophil Percentage				
<2%	18 (54,5%)	4 (30,8%)	14 (70%)	*0,05*[c]
2% < % eosinofil ≤ 5%	11 (33,3%)	7 (53,8%)	4 (20%)	
5% < % eosinofil ≤ 10%	1 (3,1%)	1 (7,7%)	0 (0%)	
10% < % eosinofil	3 (9,1%)	1 (7,7%)	2 (10%)	

[a]Fisher's exact test; [b]Mann-whitney test; [c]Kruskal-Wallis test; [d]Chi-Square test

Table 2: Crosstabulation JESREC score and Endotype of Patients with Primary CRS

		Endotype		Total	p
		Type 2	Non-type 2		
JESREC Score	eCRS	8 (24,2)	2 (6,1)	10 (30,3)	0,45[a]
	Non-eCRS	5 (15,2)	18 (54,5)	23 (69,7)	
Total		13	20	33	

[a]Mc.Nemar test

DISCUSSION

Chronic rhinosinusitis remains a burden in healthcare and socioeconomic system. Although it is understood as sinonasal symptoms, CRS is as complex disease with broad inflammatory spectrum and it became a challenge for clinician especially among otolaryngologist to determine effective treatment strategy. Former CRS classification based on the presence or absence of nasal polyps is still widely accepted, but this phenotype cannot explain the underlying cellular and molecular processes. Currently, studies on endotypes in CRS continue to develop in obtaining appropriate and targeted management strategies for CRS patients. Thus, CRS is currently known as a heterogeneous disease, that consists of several phenotypic variations caused by different cellular and molecular processes. With this new paradigm, the concept of CRS as heterogeny encourages various studies on the identification of endotypes in CRS, with expectations that it can lead to better CRS management strategies.[9]

This study found no significance between sexes and CRS prevalence, nor the JESREC score and endotype. This is similar to prospective study conducted by Ramos *et al*., on 520 patients with CRS, where the prevalence of CRS in female patients was 50.9%. This showed that there was no difference in the prevalence of CRS between the sexes of women and men.[10] Data on the prevalence of CRS in Indonesia is still limited. A study conducted at Dr. Mohammad Hoesin, Palembang found that the prevalence of CRS was higher in men compared to women with a ratio of 1.4:1.[11] In study conducted by Benjamin *et al*., prevalence of CRS found to be higher in women rather than men because of higher asthma comorbid in women.[12]

This study also found no significance between age and CRS endotype. Based on study conducted by Vaitkus *et al*. and Larsen *et al*., aging in sinonasal barrier mucosa play a role in CRS pathogenesis and it was found that nasal polyps were more prevalent among elderly. Furthermore, those studies found that aging itself was not the main factor in CRS endotype and phenotype.[13,14]

Nasal blockage was the main chief complaint identified in this study among type 2 and non-type 2 endotype, whereas there is no olfactory dysfunction found as chief complaint. It is reported that as many as 60-80% of CRS patients experienced olfactory dysfunction that tend to be mild in severity. This underlies the absence of olfactory dysfunction as chief complaint in this study. Because of its highly subjectivity, an objective method in examining olfactory dysfunction is needed such as smell identification test and sniffin stick test which support each other with imaging modalities.[15,16] In previous studies, nasal blockage was the predominant complaint in CRS patients, however, variations in CRS complaints between individu did not significantly affect the severity of CRS.[17] A study conducted in Japan stated that nasal blockage and olfactory dysfunction such as hyposmia were closely related to CRS with nasal polyps, and the presence of these two prominent complaints raises the suspicion of eCRS. Until now it is not well understood whether nasal blockage and hyposmia are clinical symptoms that are pathognomonic for type 2 endotype, or whether these symptoms are caused by the presence of nasal polyps.[18]

This study is the first study to compare the JESREC score with CRS endotype using biomolecular examination with ELISA method. Conformity test using Mc.Nemar showed no difference between the JESREC score and CRS endotype with an accuracy of 78.8%. Furthermore, the accuracy of the JESREC score in diagnosing eCRS as type 2 endotype is 24.2%, and the accuracy in diagnosing non-eCRS as non-type 2 endotype is 54.5%. This shows that the accuracy of the JESREC score in diagnosing a non-eCRS as non-type 2 endotype is higher than diagnosing an eCRS as type 2 endotype, with a probability value of 54.5%. This stated that in this study the accuracy of the JESREC score in diagnosing non-type 2 endotype was better than type 2 endotype.

Heterogeny in CRS is the basis of the accuracy value in this study. Based on EPOS 2020 primary CRS classification, allergic fungal rhinosinusitis (AFRS) and central compartment atopic disease (CCAD) were another phenotype of type 2 endotype beside eCRS.[6,19] The AFRS itself was commonly found

in southern countries with high humidity levels, especially Africa and America, and is rarely found in Indonesia. From Bent and Kuhn's diagnosis criteria for AFRS, it was found that, all diagnostic criteria are also included in the JESREC scoring criteria, in that case there is still a possibility that type 2 endotype was not eCRS in phenotype even though the JESREC score shows suspicion of eCRS.

Central compartment atopic disease (CCAD) is a variant of type 2 CRS that is closely related to allergic rhinitis with the presence of polypoid edema on middle turbinate and mucosa that outlined the skull base and orbit.[20] Just like eCRS, CCAD shows involvement of the paranasal sinuses with bilateral predominance, more opacification in the ethmoid sinuses compared to the maxillary sinuses, and has nasal polyps features on nasoendoscopy, this also explains the low percentage of accuracy of the JESREC score in diagnosing a type 2 endotype that is, due to phenotypic variation in type 2 CRS.

The phenotype of non-type 2 inflammation consists of isolated sinusitis and non-eCRS. Included in the condition of isolated sinusitis are isolated frontal disease, isolated sphenoid disease, and ostiomeatal complex involvement. Tissue remodeling characterized with basement membrane thickening without the involvement of eosinophils or IgE was the underlying pathogenesis in this phenotype. It is often found incidentally on CT-scans, because nasoendoscopy findings are atypical and can be normal. In ostiomeatal complex involvement, there is remodeling of OMC which can interfere anterior sinus group drainage so that, on a CT scan, opacification can appear in the maxillary sinus.[21,22] In non-eCRS, neutrophils play a dominant role in inflammatory process rather than eosinophil. Non-eCRS may have nasal or mucosal polyps with polypoid edema but do not have allergic mucin features. Mucin in non-eCRS tends to be thick and mucopurulent, secondary to obstruction of sinus drainage. Radiologically, similar as eCRS, non-eCRS can appear as pansinusitis features with high LMS.[23] In this study, a total of 6.1% of samples with JESREC score showed eCRS had non-type 2 endotype. This showed that non-type 2 endotype possibly had non-eCRS phenotype that overlap with eCRS clinical features. The condition of isolated sinusitis, especially frontal and sphenoid disease was not identified in this study because these sinuses do not drain to the uncinate process.

In this study, the JESREC score had a sensitivity of 61.5%, with a specificity of 90%. Study by Tokunaga *et al*., stated that the sensitivity of the JESREC score was 83% with a specificity of 66%. These findings were differ due to the differences in the number of populations included in the study, as well as in the reference standard used, where Tokunaga *et al*., used mucosal tissue eosinophils examination with histopathological HE staining as the reference standard.[24] In this study, a specificity of 90% was obtained, which means that the ability of the JESREC score to produce a score <10 among subjects with non-type 2 inflammation was 90%, while the remaining 10% were false positives. A sensitivity of 61.5% means that the ability of the JESREC score to produce a value > 11 among subjects with type 2 inflammation is 61.5%, while 38.5% is false negative. The positive predictive value (PPV) in this study was 80%, which means that the probability of type 2 inflammation when the JESREC score > 11 (eCRS) is 80%, while the negative predictive value (NPV) is 78% which means the probability of non-type 2 inflammation when the JESREC score < 10 (non-eCRS) is 78%. These two values were influenced by the prevalence of the disease, where the more the number of subjects involved in this study, the greater the PPV and the smaller the NPV. The sensitivity, specificity, PPV, and NPV showed that the JESREC score is better for screening/ rule out purposes rather that diagnostic/ tule in purposes. In clinical application, this means that, when the JESREC score shows non-eCRS, a patient does not need to perform other tests to prove that it correctly has non-type 2 endotype. Meanwhile, when the JESREC score shows eCRS, a patient still needs to perform other tests to further lead to type 2 endotype or what is called a simultaneous/parallel combination screening test.

Based on EPOS 2020, functional endoscopic sinus surgery (FESS) was the mainstay operative strategy in poorly controlled CRS after maximum appropriate medical treatment.[6] The parallel combination test to increase sensitivity value of JESREC score can include preoperative, intraoperative, and postoperative test such as skin prick test, spirometry examination for asthma status, and CT-scan of the paranasal sinuses that include oblique aspect of the middle turbinate bone. In addition, the demographic and environmental difference between Japan and Indonesia showed that further study is needed to determine the cut off for serum eosinophil percentage that represent Indonesian population. Intraoperatively, HE staining for sinonasal mucin can help diagnosing endotype. A constant follow up and recurrency monitoring postoperatively can also help diagnosing CRS endotype, because type 2 CRS esp-ecially eCRS tends to recur and refractor.

The implications for the CRS management strategy from the results of this study are the consideration of performing surgery (FESS) according to indications followed by long-term administration of macrolides with the purpose of providing good disease control in individuals with non-eCRS (JESREC score < 10).

CONCLUSION

JESREC score has conformity with endotype examination and can be use as screening method for CRS endotype. Further study is still needed to increase sensitivity of JESREC score, especially in the clinical aspects that represent Indonesian population.

CONFLICT OF INTEREST

There are no conflicts of interest.

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