ORIGINAL ARTICLE

Correlation Between Bone Morphogenic Protein-2 (BMP-2) Levels With Global Osteitis Scoring Scale (GOSS) and Endotype Biomarkers in Chronic Rhinosinusitis

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ABSTRACT

Introduction: Chronic rhinosinusitis (CRS) is a nasal and sinus inflammation. It's divided into primary and secondary types, distinguishable by biomarkers. In general, endotypes in primary CRS classified into type 2 and non-type 2 (combination of type 1 and type 3) based on specific inflammatory mediators, immune cells, and physiological functions. Paranasal sinus osteitis, a bone change due to inflammation, occurs in primary CRS marked with the damage of lamellar bone structure and new bone formation. Bone morphogenetic protein 2 (BMP-2) is a potential biomarker for bone formation in CRS. Osteitis severity is measured by the Global Osteitis Scoring Scale (GOSS). This study aims to analyze the correlation between BMP-2, GOSS, and inflammation subtypes in primary CRS. **Methods:** An analytic, cross-sectional study was conducted on 33 primary CRS patients. BMP-2 and endotype biomarkers were measured in uncinate process tissue using ELISA. Normal BMP-2 and endotype biomarkers levels were determined from non-CRS nasal tissue. Osteitis was evaluated using CT scans and GOSS. **Results:** BMP-2 level has no significant difference in endotype 2 and non-type 2 CRS. BMP-2 level had a significant correlation with IL-5 (endotype 2) (p value = 0.00) and OSM (non-type 2) (p value = 0.00). BMP-2 did not correlate with GOSS values in endotype 2 or non-type 2. **Conclusion:** Type 2 CRS had slightly higher BMP-2 levels, correlating more with IL-5 and OSM. However, BMP-2 did not correlate with osteitis severity (GOSS), suggesting a minor role in CRS osteitis.
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INTRODUCTION

Chronic rhinosinusitis (CRS) is a condition characterized by inflammation of the nasal passages and sinuses, lasting at least 12 weeks. Common symptoms include nasal congestion, rhinorrhea, facial pain, and loss of smell. Endoscopic examination may reveal nasal polyps, mucus, or swelling in the sinuses. CT scan examination revealed changes in mucosal, osteomeatal complex and/or
sinuses.(1)

CRS can be categorized into CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). The estimated average incidence of CRS is 83 ± 13 cases of CRSwNP per 100,000 people/year and 1048 ± 78 cases of CRSsNP per 100,000 people/year.(1) Maharani et al. found that in Dr. Saiful Anwar General Hospital, Indonesia, CRSwNP patients range at the age of 16-30 years old (36.7%) and majority CRSsNP patients at the age of 46-60 years old (36.4%). There were 44 males (44.9%) and 54 females (55.1%) included in this study with chief complaint of nasal blockage in both CRSwNP (72.1%) and CRSsNP (35.2%).(2)

According to EPOS 2020, CRS can be divided into primary and secondary CRS. Primary CRS is contemporarily defined as a primary inflammatory disorder of "the airway" or respiratory system. While secondary CRS occur when their sinonasal mucosal disease is secondary to another process such as a dental infection, fungal infection, a deviated nasal septum, nasal polyps, cystic fibrosis, or an immune deficiency. (3) Primary CRS can be further classified as Type 2 (eosinophilic) or non-Type 2 (neutrophilic) depending on the type of inflammatory cells and biomarkers involved. (1) There are three types of inflammation in CRS, namely type 1 with Th1 dominance (increase in neutrophils, IFN-c, IL-2, and TNF-α), type 2 with Th2 dominance (hyperactivity of eosinophils and IL-4, IL-13, IL-5, IL-10, IL-13), and type 3 with Th17 dominance (increased IL-

6, IL-17, IL-22 and TNF-α).(4) Kato et al. recommend several main biomarkers to identify endotypes in CRS with and without nasal polyps. For type 1 inflammation, the main markers are IFN-γ and CXCL 10, for type 2 with CLC and ECP markers, for type 3 with IL-17A and GCSF markers. In CRS, chronic activation of one or more endotypes in sinonasal tissue generally occurs.(5)

Paranasal sinus osteitis is a relatively new clinical finding, describing changes in the bone due to inflammation that will damage the lamellar bone structure and the formation of new bone.(6) Osteitis is often found in CRS patients and is associated with disease severity and cases that are difficult to treat.(7) The pathogenesis and epidemiology of osteitis in CRS includes clinical and biological aspects such as history of previous surgery, severity of CRS, inflammatory pattern of CRS, and biofilm formation. The biomolecular mechanism of osteitis in CRS is actually still not completely clear, but recent research shows that there is a process of neo-osteogenesis and bone remodeling in osteitis in primary CRS.(8) The bone thickening process in CRS with osteitis is related to Runtrelated transcription factor 2 (RUNX2), which is a transcription factor that has a function in the induction, proliferation and maturation of osteoblasts.(9)

Bone morphogenetic protein 2 (BMP-2) is a potential biomarker in CRS. BMP-2 is part of the Transforming Growth Factor-β (TGF-β) superfamily and is known to be a key regulator of osteogenesis. BMP-2 acts selectively on type I and type II BMP receptors, and initiates osteogenesis by regulating osteogenic transcription such as RUNX2.(10)

Various studies show that CRS with type 2 inflammation, especially Eosinophilic Chronic Rhinosinusitis (ECRS) has the most mucosal damage and osteitis compared to other types of CRS. Induction of TGF-β production and osteoblast activation by eosinophils has been linked to increasing the severity of osteitis in ECRS patients.(11)

Computed tomography (CT) presents a minimally invasive imaging alternative and remains the most useful modality for imaging the paranasal sinuses. Osteitis is defined as irregular bony thinning and/or thickening of the sinus walls along with focal sclerosis or focal damage (demineralization, loss of trabeculae, cortical damage, loss of structures or landmarks).(8)

Measuring bone thickening has become a widely used form of osteitis assessment. This measurement can be done using a CT scan modality.(8) Global Osteitis Scoring Scale (GOSS) characterizes ten sinuses in terms of bone thickness and percentage of bone wall involvement, markers of severity and extent, respectively.(6) Bilateral frontal sinuses, anterior ethmoid sinuses, posterior sinuses, maxillary sinuses, and sphenoid sinuses were evaluated individually and ranked from 0 to 5. Then the scores of each sinus were added to create a total score. The classification of osteitis can be divided based on the total score, namely Mild = 5–20, Moderate = 20–35, and Severe = >35.(12) The use of GOSS can help clinicians determine the degree of osteitis in patients with CRS. GOSS scoring can be seen in Table 1.

Table I : The Global Osteitis Scoring Scale

Paranasal Sinus	Side	Score	Total per Sinus
Maxillary	D		
	S		
Frontal	D		
	S		
Anterior Ethmoidal	D		
	S		
Posterior Ethmoidal	D		
	S		
Sphenoidal	D		
	S		
	Total		
	Degree		

Osteitis on CT scan is characterized by loss of bone definition, hyperostosis, new bone formation, or signs of heterogeneity in each
paranasal sinus walls
Osteitis Score:
1) <50% of the sinus wall is involved and the thickness of the osteitis is <3 mm
2) <50% of the sinus wall is involved and the osteitis is 3-5 mm thick
3) <50% of the sinus wall is involved and osteitis thickness is >5 mm, or >50%
the sinus wall is involved and the thickness of the osteitis is <3 mm
4) >50% of the sinus wall is involved and the osteitis is 3-5 mm thick
5) >50% of the sinus wall is involved and the thickness of the osteitis is >5 mm
An assessment of the maxillary, frontal, anterior ethmoidal sinuses, ethmoidalis posterior, and sphenoidal sinus, right and left sides
Osteitis degree:
<5 = not significant, 5-20 = mild osteitis, >20-35 = moderate osteitis, >35 = severe osteitis

Until now, there has been no research examining the relationship between BMP-2 and GOSS on endotypes in CRS. Therefore, in this paper, we will examine the relationship between BMP-2 and endotypes in CRS, as well as the relationship between GOSS values and endotypes in CRS.

MATERIALS AND METHODS

Samples

Uncinate process of maxillary sinus was harvested during Functional Endoscopic Sinus Surgery (FESS) in Dr. Saiful Anwar General Hospital after obtaining the written informed consent from patients from December 2022 to June 2023. The inclusion criteria for samples is Adult patients > 18 years old who meet the diagnostic criteria for primary CRS based on symptoms and clinical

features according to the EPOS 2020, and exclusion criteria are patients with secondary CRS, CRS involving the posterior paranasal sinuses only, CRS patients who have undergone a previous FESS procedure, and CRS patients who have used systemic or local corticosteroids or systemic antibiotics within 4 weeks before taking the specimen. Samples were transported on ice from Dr. Saiful Anwar General Hospital to Laboratory of Biomedicine Medical Faculty Brawijaya University Malang using a leak-proof cooler box. Thirty three (33) uncinate process samples were collected, each sample tested with ELISA Kit 96T CLC, ECP, IL-5, IFN-γ, OSM, IL-17A, and BMP-2 (Finetest). We use CLC, ECP and IL-5 as the biomarkers for type 2 while IFN-γ, OSM, IL-17A were the biomarkers we use to identify non type 2 endotype. Paranasal sinuses CT scans were taken at Radiology Installation in Dr. Saiful Anwar General Hospital and processed with HOROS 3.3.6 software to calculate the GOSS. The approval and ethical clearance from the Ethics commission of Dr. Saiful Anwar General Hospital Malang was attained upon commencement of the study [Reference No: 400/162/K.3/102.7/2022 – 1 Agustus 2022].

Control for normal cut off level of endotype biomarkers and BMP-2

We used the tissue taken from nasal cavity mucosa with inclusion criteria of adult patients aged >18 years, diagnosed with a deviated nasal septum and/or hypertrophy nasal turbinates and indicated to underwent septoplasty and/or turbinoplasty. Exclusion criteria are patients with allergic rhinitis, patients who used corticosteroids or antibiotics within 4 weeks before specimen collection.

ELISA examination for biomarkers and BMP-2

After tissue preparation and weighing, the samples then were homogenized with a ratio of 600 ul PRO-PREP per 10 mg tissue, followed by incubation for 20-30 minutes in a -20°C refrigerator to induce cell lysis. Samples subjected to centrifugation at 13,000 rpm for 5 minutes at 4°C and the supernatant is transferred to a tube. Standard, sample and control wells on a pre-coated plate are prepared, with each position noted. Divide 100 ul from tubes 0, 1, 2, 3, 4, 5, 6, and blank into standard wells then 100 ul of diluted sample to the sample well added. Samples then incubated at 37°C for 90 minutes. 100 ul biotin-labeled antibody working solution were added to the standard, sample and control wells, and placed at the bottom of each well without touching the walls, cover the plate and incubate at 37°C for 60 minutes. 100 ul HRP-Streptavidin Conjugate working solution were added to each well and incubated at 37°C for 30 minutes, and washed 5 times with wash buffer, and let the wash buffer remain in the well for 1-2 minutes each time. 90 ul TMB substrate was added to each well and incubated at 37°C for 10-20 minutes. 50 ul stop solution was added to each well, the color then changed to yellow. Read the optical density (OD) absorbance at 450 nm in a microplate reader immediately after adding the stop solution.

GOSS Examination

CT scans of paranasal sinuses were taken without contrast, bone setting, in axial, coronal and parasagittal sections, with thickness of 1-3 mm. DICOM of CT scans were imported into HOROS 3.3.6 software. Calculation of each component and total GOSS was carried out using HOROS 3.3.6 software. Each paranasal sinus is assigned a value: 1 = less than 50% of the sinus wall is involved and the osteitis is <3 mm thick; 2 = less than 50% of the sinus wall is involved and the osteitis is 3-5 mm thick; 3 = less than 50% of the sinus wall is involved and the osteitis is thick, bone thickening is >5 mm or more than 50% of the sinus wall is involved and the osteitis is <3 mm thick; 4 = more than 50% of the sinus wall is involved and the osteitis is 3-5 mm thick; 5 = more than 50% of the sinus wall is involved and the osteitis is >5 mm thick. The paranasal sinuses assessed were the frontal, anterior ethmoidal, posterior, maxillary and sphenoidal sinuses on the right and left sides, with total of 10 sinuses assessed. The score range is 0-50. Total score of <5 = not significant, 5-20 = mild osteitis, >20-35 = moderate osteitis, >35 = severe osteitis. The osteitis and the GOSS was determine with one radiologist expertise.

Data analysis

Categorical descriptive data will be presented in the form of a frequency distribution table (percentage), numerical data will be presented in the form of a measure of central tendency (minimum, maximum, median, average and standard deviation values). The correlation between BMP-2 and endotype biomarkers in CRS will be analyzed using the Pearson test if the distribution is normal, and Spearman if the distribution is not normal. The correlation between BMP-2 and GOSS values in CRS will be analyzed using the Spearman test. Data analysis uses a 95% confidence level, α=0.05, and determined as significant if $p<0.05$. Analysis was carried out with SPSS 25 for Windows software.

RESULTS

The characteristics of the study sample include age, gender, main complaint, and duration of complaint. The average age of the sample was 38.36±15,272 years with an age range of 18-68 years, a median of 32 years, with female sex as many as 21 (63.6%). Most patients came with the main complaint of nasal congestion (18 patients or 54.5%). The average duration of complaints felt by patients was since 91.2±109.9 weeks ago and a median of 52 weeks.

Biomarker Levels in CRS

The biomarker proteins used in this study were Eosinophil Cationic Protein (ECP), Charcot Leyden Crystal (CLC) and IL-5 for CRS Type 2 and Interferon γ

(IFN-γ), OSM and Interleukin 17A (IL-17A) for CRS Non-type 2. Tissue samples were taken from the uncinate process. Biomarker levels in CRS can be seen in table 2.

Table II : Biomarker levels in CRS

Biomarkers	Minimum	Maximum	Mean
Type 2			
CLC (ng/mL)	0.142	0.1850	0.492 ± 0.363
ECP (pg/mL)	83,810	571,749	353.31 ± 132,862
IL-5 (ng/mL)	3,985	309,201	64,872 ± 92,456
Non-type 2			
IFN- (ng/mL)	14,516	43,392	20,267 ± 5,530
OSM (pg/mL)	22,180	1577,563	292,352 ± 440,260
IL-17A (pg/mL.)	20,604	187,174	49,916 ± 33,563

Note : CLC = Charcot-Leyden Crystal, ECP = Eosinophil Cationic Protein, IL-5 = Interleukin 5, IFN - = Interferon Gamma, OSM = Oncostatin M, IL-17A = Interleukin 17A

Our analysis revealed a diverse distribution of inflammation types, with 1 type 2 (3%), 2 non-type 2 (6%), 16 mixed type 2 (49%), 13 mixed non-type 2 (39%), and 1 untypeable sample (3%). Based on these result, tissue samples can be divided into type 2 (≥342.22) and non-type 2 (<342.22), obtained as many as 19 type 2 inflammatory samples and 14 non-type 2 samples. We divided the samples into two groups to further test the correlation of BMP-2 levels with ECP, CLC, and IL-5 (type 2 group), as well as the correlation of BMP-2 levels with IFN-γ, OSM, and IL-17A (non-type 2 group).

BMP-2 levels in CRS

BMP-2 biomarkers were obtained from the uncinate process and processed with ELISA. BMP-2 levels obtained in this study can be seen in table 3. BMP-2 levels tended to be higher in type 2 inflammation with an average of 3.55 ± 5.76 ng/mL, while in non-type 2 an average of 1.26 ± 2.54 ng/mL. Based on different tests using the Mann Whitney method, a p value of 0.282 (>0.05) was obtained or no significant difference was found between increased levels of BMP-2 in type 2 and non-type 2 inflammation.

Table III : BMP-2 levels in CRS.

Biomarkers	Minimum	Maximum	Mean
Type 2	0.1	19.20	3.55 ± 5.76
Non-type 2	0.09	9.72	1.26 ± 2.54
Total (ng/mL)	0.09	19.20	2.57 ± 4.75

Osteitis in CRS based on GOSS

The average GOSS score obtained is 16.151 ± 10.146, minimum value 3 and maximum 41. From all study samples, 5 (15.2%) samples of meaningless osteitis, 16 samples (48.5%) of mild osteitis, 11 samples (33.3%) of moderate osteitis, and 1 sample (3%) of severe osteitis were obtained. Details of GOSS results can be seen in Table 4.

Table IV : Descriptive GOSS result in CRS

GOSS	Total
Mean	16,15
SD	10,14
Minimum	3
Maximum	41
Degree, n (%)	Total
Meaningless (<5)	5 (15,2%)
Mild (5-20)	16 (48,5%)
Moderate (21-35)	11 (33,3%)
Severe (>35)	1 (3%)

Correlation of BMP-2 with Endotype 2 and Non-type 2 Biomarkers

Details of BMP-2 with endotype 2 and Non-type 2 biomarkers correlation can be seen in Table 5. In the Spearman correlation test, significant test results were obtained (p value 0.000 or <0.01) or there was a significant correlation between BMP-2 and IL-5 levels. In the Spearman correlation test, significant test results were obtained (p value 0.000 or <0.01) or there was a significant correlation between BMP-2 and OSM levels.

Table V : Correlation between Endotype type 2 and non-type 2 biomarkers levels to BMP-2 levels in CRS

Biomarkers	BMP-2 (p value)
Type 2	
CLC	0,75
ECP	0,24
IL-5	<0,05*
Non-type 2	
IFN-	0,45
OSM	<0,05*
IL-17A	0,21

Note : CLC = Charcot-Leyden Crystal, ECP = Eosinophil Cationic Protein, OSM = Oncostatin M

* : Significant

Correlation of BMP-2 Levels to Osteitis based on GOSS

Based on the normality test, it was found that the distribution of GOSS values was abnormal, so the Spearman test was carried out. There was no significant result (p >0.05) or there was no correlation between BMP-2 levels and GOSS values in overall CRS and in specifically type 2 and non-type 2 CRS. BMP-2 and GOSS correlation can be seen in Table 6.

Table VI : BMP-2 and GOSS Correlation in CRS

	BMP-2 (p value)	BMP-2 (Type 2)	BMP-2 (Non-type 2)
GOSS	0,57	0,68	0,61

DISCUSSION

We used IFN-γ, OSM, and IL-17A to assess non-type 2 immune responses in this study. Type 2 immune response is characterized by the production of IL-4, IL-5 and IL-13 from ILC2s, Tc2 cells, and Th2 cells. The presence of CLC in tissues and body fluids is associated with local eosinophilia. ECP is produced as a result of eosinophilic activation and inflammation. Because of their association with eosinophils, CLC and ECP are associated with type 2 inflammation. The biomarker proteins used in this study to assess type 2 immune responses were ECP, CLC and IL-5. In our study we found most of our samples have a mixed type inflammation pattern. With slight tendency towards the type 3 endotype. How exactly should we define mixed type remain obscure and its impact to precision therapy in the future needs further researches.

BMP-2 levels in type 2 inflammation were higher than non-type 2 inflammation in this study. Based on the difference test, there was no significant difference between increased BMP-2 levels in type 2 and non-type 2 inflammation. This result can be caused by differences in the number of samples, namely 19 type 2 inflammatory samples and 14 non-type 2 samples. BMP-2 levels are thought to be higher in CRS type 2 because according to theory, the main cell source of BMP-2 is eosinophils, which is the basis of the pathophysiology of CRS type 2.(10) This theory implies that the more eosinophils involved in the inflammatory response, the greater the BMP-2 levels produced. However, BMP-2 cell sources are not only derived from eosinophils, but can also come from M1 macrophages.

Kim examined BMP-2 and BMP-7 levels in CRS and stated that BMP-2 and BMP-7 levels in uncontrolled CRS patients' nasal polyps were higher than levels in the uncinate process. Kim also found BMP-2 and BMP-7 results associated with refractory CRS. Kim's study examined BMP-2 and BMP-7 levels in CRS, but the samples used were taken from uncinate process and nasal polyps.(10) Differences in sampling locations, sample characteristics cause the two studies cannot be compared directly.

Research by Georgalas showed an average GOSS score of 9.2 ± 14.2, in 102 samples.(13) The rate of osteitis in this study sample was higher than in Georgalas' study. Based on Osteitis assessed by GOSS is divided in severity into meaningless osteitis, mild, moderate, and severe degrees. In this study, 5 samples (15.2%) of meaningless osteitis (GOSS <5), 16 samples (48.5%) of mild osteitis (GOSS 5-20), 11 samples (33.3%) of moderate osteitis (GOSS 21-35), and 1 sample (3%) of severe osteitis (GOSS >35). Another study by Aparna on 31 samples, found that the highest percentage of osteitis in CRS patients was mild osteitis (51.6%), then moderate osteitis (45.2%), and severe osteitis (3.2%).(14) Based on comparisons with Aparna's study, there was a similarity in the distribution of the severity of osteitis in the samples.

In this study, the test results were not significant or there was no significant correlation between BMP-2 with CLC (p value 0.757) and ECP (p value 0.248) levels. Based on the hypothesis, CLC and ECP which are products of active and degranulated eosinophils, are considered biomarkers that express an increase in type 2 inflammation associated with an increase in BMP-mediated osteitis, specifically BMP-2 because eosinophils are one of the cellular sources of BMP. (10) However, in this study no correlation was found between the two, possibly caused by an increase in other types of BMP other than BMP-2, because BMP is a superfamily consisting of various types of BMP that have their respective functions.(10) In the absence of correlation results between BMP-2 and CLC and ECP, further research is needed on the role of CLC and ECP on the pathophysiology of osteitis.

In this study, very significant test results were obtained (p value 0.000 or <0.01) or there was a significant correlation between BMP-2 and IL-5 levels. IL-5 protein for eosinophil recruitment and activation is a biomarker that plays a role in the pathogenesis of CRS type 2.(15) Eosinophils themselves are the cellular source of the BMP-2 protein.(10) Based on testing, elevated IL-5 levels correlate with increased BMP-2 levels. Therefore, if there is an increase in IL-5 levels in CRS inflammation, eosinophil levels also increase, thus increasing BMP-2 levels which are products of eosinophils.

This study used biomarkers IFN-γ, IL-17A, and OSM as markers of non-type 2 inflammation. In type 1 inflammation, IFN- γ functions in epithelial barrier damage by damaging epithelial cell tight junctions, decreasing transepithelial resistance, and inducing apoptosis of nasal epithelial cells. IL-17A is involved in type 3 inflammation and can mediate α oncogenes and IL-8-related growth to stimulate the nasal mucosa, accelerate fibroblast growth and induce tissue remodeling.(16) In this study there was no correlation between BMP-2 levels with IFN- γ and IL-17A, with the possibility that increasing IFN- γ and IL-17A not only

increased BMP-2 levels, but increased levels of other types of BMP such as BMP-7 and BMP-10, and further research is needed on the role of IFN- and IL-17A in osteitis.

Based on testing, very significant correlation results were obtained between BMP-2 and OSM. OSM causes epithelial barrier changes by reducing tight junctions. (17) However, until now there has been no theory that explains the direct correlation between OSM and BMP-2 that causes osteitis in CRS. Research by Kim et al. using samples from nasal polyp tissue found a correlation between BMP-2 and IL-17A. Kim also looked for a correlation between BMP-2 and IFN- ɣ, but there was no correlation between the two.(10) Until now, there have been no other studies looking for a correlation between BMP-2 and OSM. The results of correlation testing between BMP-2 and biomarkers that have proven to be significantly correlated, namely IL-5 and OSM, are expected to be new knowledge for the ORL-HNS field in curative and preventive on the management of osteitis in CRS.

Theoretically, BMP-2 levels are associated with osteitis through persistent mucosal inflammation that results in bones at the base of the mucosa cannot grow properly, causing neoosteogenesis which increases bone thickness. BMP-2 is produced mainly during inflammation of CRS. Dendritic cells through T cells then mediate TH2. TH2 produces IL-4, IL-13, and IL-5, then eosinophils, neutrophils and macrophages are formed. The production of BMP-2 is influenced by inflammatory cytokines which then regulate SMAD6 to signal BMP-2 which may lead to bone remodeling and osteitis.(10) In Kim et al's study, BMP-2 was correlated with GOSS with p value = 0.003, but the study sample came from the nasal polyp tissue of CRS patients with nasal polyps. Based on the test results, there was no correlation between BMP-2 and GOSS levels (p value = 0.57). Due to the many stages required from BMP-2 to osteitis, it is possible that there are other BMPs that are directly and significantly correlated with osteitis which calculated using GOSS.

CONCLUSION

In our research BMP 2 level were slightly higher in the type 2 CRS and correlates more with IL-5 and OSM compares to other 4 endotype biomarkers. We also found that the elevation BMP 2 does not correlate with GOSS degrees in type 2 and non-type 2 CRS, so we concluded that BMP 2 does not have a major role in osteitis of CRS. To define the exact role of BMP 2 in the pathomechanism of CRS especially in the type 2 inflammation requires further research in the future.

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