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The Diagnostic Value of Serum Eosinophil Cationic Protein for Aspirin Intolerance in Patients with Chronic Rhinosinusitis

Abstract

Objective: Aspirin intolerance (AI) is one of the endotypes of chronic rhinosinusitis (CRS) that can be effectively treated if detected early. Considering the limitations of the available tests for AI, there is still a need for an affordable, cost-effective, and safe marker that can enhance AI's early detection. In the past years, the association between AI and eosinophilic inflammation has been well documented. Eosinophil cationic protein (ECP) is a specific marker for eosinophil activation. In this study, we aimed to assess the value of assaying serum ECP in detecting AI in patients with CRS.

Methods: Eighty-four patients with CRS were enrolled in this study, and they underwent an intravenous or oral aspirin (ASA) challenge test. Receiver operating characteristic curves were used to evaluate the diagnostic value of serum ECP level for the AI in patients with CRS and calculate the best diagnostic cut-off value.

Results: Using systemic ASA provocation, the prevalence of AI among patients with CRS was relatively high (43%). There was a significant difference in the mean serum ECP level in the two groups (positive group 19.3, negative group 8.6 µg/L, and $P < .0125$). Serum ECP level showed an acceptable discrimination value for predicting AI in patients with CRS (area under the curve = 0.622). The best diagnostic cut-off value and corresponding sensitivity and specificity were >13.9 µg/L (38.89%, 85.42%).

Conclusion: Assaying serum ECP in patients with CRS could help detect AI, especially when other more accurate tests are not available.

Keywords: Aspirin intolerance, chronic rhinosinusitis, eosinophil cationic protein, systemic aspirin challenge test

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Introduction

The symptomatic inflammation of the paranasal sinuses and the nasal cavity is called rhinosinusitis. The term rhinosinusitis is preferred over sinusitis because the mucosa of the nasal cavity is also affected by inflammation. According to the American Academy of Otolaryngology-Head and Neck Surgery, chronic rhinosinusitis (CRS) is defined as the presence of at least two out of four cardinal symptoms (i.e., facial pressure/pain, hyposmia/anosmia, nasal congestion, and nasal discharge) for a minimum of 12 consecutive weeks, in addition to objective evidence on clinical examination or radiography. CRS has a significant socioeconomic implication. According to a survey done in the USA in 2007, approximately $8.3 billion is spent annually on CRS, on primarily drug prescriptions and outpatient care. The average cost of surgery is $7700 per patient.[1-4]

The indirect cost of CRS is substantial and more important than the direct cost. CRS accounts for one to two lost workdays per patient per year and 73 million days of restricted activity.[5,6] It also substantially impacts the quality of life through chronic symptomatology and acute exacerbations of nasal and pulmonary symptoms.

Chronic rhinosinusitis is not a single disease, but it results from different pathogeneses that lead to chronic sinonasal inflammation. With the developments in our understanding of CRS pathophysiology, the focus is placed nowadays on classifying patients with CRS according to the underlying inflammatory mechanisms driving the disease (endotypes), which are much more likely to be predictive of long-term disease prognosis and response to treatments.[7]

The chronic hyperplastic eosinophilic rhinosinusitis associated with aspirin intolerance (AI) is one of CRS's refractory endotypes. This endotype is associated with nasal polyposis, which frequently fills all sinuses and may even destroy bone structures. Nasal polyps tend to regrow, resulting in multiple sinus surgeries rapidly. These patients have a higher number of emergency interventions and hospital admissions for asthma exacerbations.[8]

According to the current clinical data, aspirin (ASA) desensitization can be regarded as an effective treatment for AI. Significant improvement in the quality of life, nasal obstruction secondary to nasal polyposis, asthma, and olfactory function has been described and well documented for patients with AI. The frequency of surgical interventions in recurrent nasal polyps was shown to decrease from one surgery every three years to one surgery every nine years.[9] Therefore, it is essential to recognize those patients with AI as it has a different and effective treatment method than other forms of CRS.

The accepted gold standard diagnostic test for AI nowadays is the systemic challenge test.[10] In some cases of CRS, a detailed history should enable the physician to diagnose AI. In unclear cases, a carefully controlled challenge test with ASA or other NSAIDs is necessary. The provocation test is performed either locally (nasal or bronchial) or systemically (oral or intravenous [IV]). The systemic provocation is the most sensitive test for a confirmative diagnosis, and a multi-systemic response is expected.

By contrast, local ASA provocation may be limited to local signs and symptoms. Despite the lower sensitivity of nasal/bronchial ASA provocation than the systemic one, the former may be chosen for its safety. The IV route is the simplest means of prompt drug delivery at a given time. Because of the fear of severe adverse reactions, the IV ASA challenge test has not been widely used in clinical practice. A multi-system challenge plus fast response would be expected to have a higher sensitivity with a shorter provocation period. According to Seong et al.,[11-14] IV ASA provocation was more efficacious than oral ASA challenge in diagnosing NSAID hypersensitivity (specificity 100%, sensitivity 93.5%, no false-positive cases, and three false-negative cases with single-NSAID hypersensitivity who did not react to the consecutive ASA oral provocation). Nizankowska et al.[15] reported that the sensitivity and the specificity of the 500 mg oral ASA challenge were 89% and 93%, respectively.

In some cases, like severe nasal obstruction, severe uncontrolled asthma, or non-compliance, provocation tests are not preferred.[16] In many cases, this in vivo test is impossible owing to a lack of specific technical and/or medical equipment (such as measuring respiratory function, vital signs monitoring, appropriate emergency unit, or intensive care unit) or inadequately trained medical staff. It is also contraindicated in pregnant women and children under 16 years of age. Numerous attempts have emerged in the past 115 years to diagnose and confirm AI by in vitro diagnostic tools. In the literature, there are approximately 12 in vitro tests for AI. Most of these tests are not widely used because of their low reliability and validity. Functional eicosanoid testing (FET) is the only in vitro test with excellent diagnostic accuracy (sensitivity 96% and specificity 83%).[17] However, this test is expensive, not usually covered by medical insurance, and is not available in all hospitals or polyclinics.

After reviewing the diagnostic tools available in the literature for diagnosing AI, it is clear that there is a need to find a diagnostic method that is reliable, safe, readily available, and cost-effective.

Eosinophil granulocytes are found in the mucous membrane of the respiratory and digestive system and lymphocyte-associated organs. The most prominent feature of eosinophils is the large secondary granules, each containing four primary proteins, the most well-known of which is the eosinophil cationic protein (ECP). This protein is used as a marker for eosinophilic diseases and is quantified in biological fluids such as sera, bronchial lavage, and nasal secretions. ECP is a neurotoxic and cytotoxic ribonuclease.[18] Elevated serum ECP levels are associated with higher eosinophil expression in nasal smears and sera and can be used as a marker for local and systemic eosinophil expression.[19] Szczeklik et al.[20] have shown that the serum level of ECP, a specific marker of eosinophil activation, is elevated during bronchoconstriction following ingestion of oral ASA. Eosinophilic rhinosinusitis with nasal polyposis, severe adult-onset asthma, and cysteinyl-leukotrienes overproduction are the hallmarks of aspirin-exacerbated respiratory disease (AERD).[21]

In this study, we assessed the value of assaying serum ECP levels (as a marker for activated eosinophils) in diagnosing AI in a cohort of subjects with CRS compared with the gold standard systemic ASA challenge.

Methods

This study is a retrospective data analysis from the hospital information system and patient files. All patients with CRS between 2013 and 2020 who underwent an IV or oral ASA challenge test in the department of otorhinolaryngology, head and neck surgery, in the German Military Hospital of Ulm were included in this study. The inclusion criteria for the study were the following: (1) clinically confirmed CRS with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP), (2) availability of IV or oral ASA provocation test with documented results, (3) availability of serum ECP results. The following exclusion criteria were applied: age <16 years, pregnancy, immunodeficiency, cystic fibrosis, and malignancy. CRS is diagnosed when the symptoms last for more than 12 weeks regardless of acute exacerbations.[22]

ECP as a cytotoxic and neurotoxic protein released in the late phase allergic reaction was measured from centrifuged blood serum using fluorescence enzyme immunoassay (ImmunoCAP® 250 system provided by ThermoFisher™) with a quantitative range of 2 to 200 µg/L. The geometric mean level was 5.5 µg/L, 95th percentile was 13.3 µg/L. Values above 11.3 µg/L (90th percentile) were considered as elevated, indicating eosinophil inflammatory activity.

We advised all patients with CRS who had more than one sinus surgery, severe polyposis, or clear history of AI to undergo an IV ASA provocation test. According to the spirometry results, the systemic provocation was carried out either orally or intravenously after obtaining written informed consent from the patients. To avoid acute pulmonary reactions that might result from IV ASA administration, patients with partially controlled or uncontrolled bronchial asthma were gradually provoked orally. Our limit to perform an IV ASA provocation was a peak expirato-

ry flow of 70% and a Tiffeneau index (forced expiratory volume in first second, concerning the forced vital capacity) of 80%. If one of these two values were under the limit or systemic steroids could only control asthma, the oral provocation scheme was used. All other patients with CRS were intravenously provoked.

The provocation test was positive if any reaction or adverse effect during the provocation was observed. A late reaction was also considered a positive test. The IV provocation was performed with 500 mg lysine acetylsalicylate powder, which was dissolved in sodium chloride 0.9% isotonic saline (250 mL) and was administered gradually via an automatic infusion device over 2 h. The provocation was stopped immediately if the patient felt any pulmonary reaction. The patients were given a form to document threshold values for nasal symptoms, nasopharyngeal symptoms (including eustachian tubes), dermatological manifestations, and pulmonary symptoms to record immediate reactions. The contraindications for performing IV provocation tests, included children under 16 years of age, pregnant women, patients with pulmonary disease (FEV1 <70%), cardiac or gastrointestinal diseases, respiratory infections in the last four weeks, and drug therapy with beta-blockers.

Sex, age, serum ECP level, and the IV or oral ASA provocation test results were collected. The collected data were presented on a Microsoft Excel® sheet, and the statistical analyses were carried out using MedCalc version 19.3.1 software and STATA version 13.0 (STATA-Corp, College Station, TX, USA).

The studied test's ability to discriminate between patients who were aspirin tolerant and intolerant was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The sensitivity, specificity, diagnostic accuracy (DA), Youden index, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated. *P* value was considered non-significant if $P > .05$, significant if $P < .05$ and highly significant if $P < .01$.

Frequencies and percentages were calculated for categorical variables. Means and standard deviations (SD) were calculated for continuous variables if the data followed a normal distribution (e.g., age). Chi-squared tests were used to compare the proportions of categorical variables between the positive and negative groups. T-tests were used to compare means between the two groups. We analyzed the rest of the data descriptively.

The ROC curves were constructed to quantitate the AUCs with a 95% confidence interval (CI). The AUC was divided into five categories, which were 0.90-1 (excellent), 0.80-0.90 (good), 0.70-0.80 (fair), 0.60-0.70 (low), and 0.50-0.60 (fail).

Results

We included 84 patients with CRS with a mean age of 44 (range: 19-81) years who met all the inclusion and none of the exclusion criteria. Fifty-three percent of the patients were aged between 31 and 55 years. There was no significant difference in age for the positive provocation group (41 years) and the negative provocation group (46 years) with $P = 0.1595$.

Unexpectedly, 31% of the study population were women (n = 26) and 69% were men (n = 58). There was a statistically significant difference between the positive and negative groups in sex $P < .0001$ (the percentage of women in the positive and negative groups was 56% and 12%, respectively). In our study, 86% of the patients (n = 72) were intravenously provoked, and 14% (n = 12) were orally provoked.

Interestingly, only 19% of the patients in the positive provocation group had bronchial asthma, whereas 27% of those in the negative provocation group were asthmatics. However, this difference was not statistically significant ($P = 0.3955$). Furthermore, the percentage of those having nasal polyps in the negative provocation group was significantly higher than those in the positive group (40% vs. 11%, $P = .0034$).

Using systemic ASA provocation as the gold standard, 43% of our patients (n = 36) were positive, and 57% (n = 48) were negative. The prevalence of AI in the study population was 42.9%. Serum ECP categorized 75% (n = 63) of the patients as negative and 25% (n = 21) as positive (serum ECP > 13.9 µg/L as the optimal cut-off point). The range of serum ECP level was 1.9-138 µg/L in the positive provocation group and 1.9-40.1 µg/L in the negative group. In addition, there was a significant difference in the mean serum ECP levels in the two groups (positive group 19.3 µg/L, negative group 8.6 µg/L, and $P < .0125$). Table 1 summarizes the characteristics of the positive (ASPT+) and negative aspirin systemic provocation test groups (ASPT−).

The discriminating ability of the serum ECP level in detecting patients with AI was assessed by plotting ROC curves, which were drawn by the sensitivity and 100-specificity at different cut-off levels (Figure 1). The AUC was 0.622, indicating a limited success of using serum ECP as a diagnostic marker for AI. The nearest point to the upper left corner of Figure 1 represents the optimal threshold (>13.9 µg/L); the corresponding sensitivity was 38.89%, the specificity was 85.42%, and the diagnostic accuracy (DA), positive predictive value (PPV), negative predictive value (NPV), PLR, and NLR were 65.46%, 66.7%, 65.1%, 2.67, and 0.72, respectively (Table 2). After constructing the ROC curve of serum ECP using the cut-off value recommended by our hospital laboratory (11.3 µg/L), there was an improvement in the sensitivity (38.89% to 47.22 %) at the cost of decreasing specificity, DA, PPV, NPV, PLR, AUC, and the significance level P compared with the best cut-off value of 13.9 µg/L (Table 3 and Figure 2). The difference between the area under the ROC curves was 0.0208 (95% CI 0.0450-0.0866) with $P = 0.5350$, statistically indicating no significant difference.

Table 1. Characteristics of the Positive (ASPT+) and Negative Aspirin Systemic Provocation Test Groups (ASPT-)

	ASPT+(43%) N = 36	ASPT-(57%) N = 48	P
Mean age (years)	41	46	.1595
Sex (men:women)	44%:56%	88%:12%	.0001*
Nasal polyp	11%	40%	.0034*
Asthma	19%	27%	.3955
Mean serum ECP (range)	19.3 (1.9−138)	8.6 (1.9−40.1)	.0125*

*$P < .05$

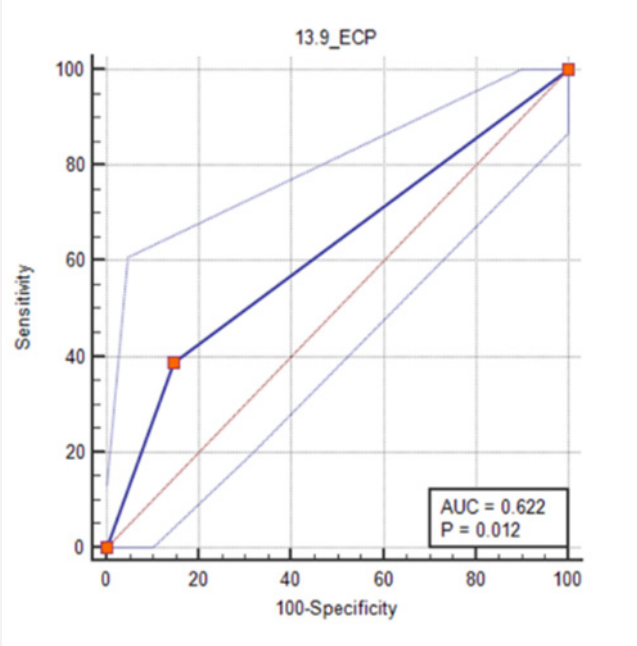

Figure 1. ROC Curve for Serum ECP Using the Optimal Cut-off Value 13.9 µg/L with 95% Confidence Interval

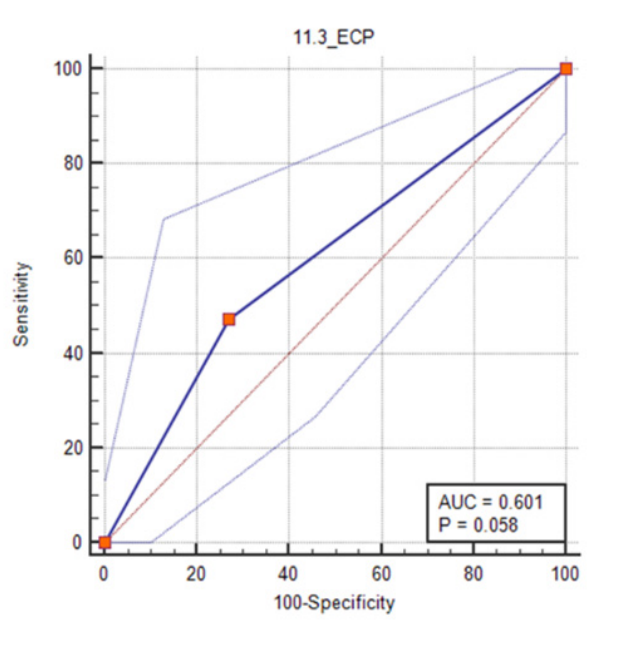

Figure 2. ROC Curve for Serum ECP using the Optimal Cut-off Value 11.3 µg/L with 95% Confidence Interval

Table 2. ROC Analysis Summary for Serum ECP Using the Systemic Provocation Test as a Gold Standard for Diagnosis of Aspirin Intolerance and 13.9 µg/L as Optimal Cut-off Value

Area under the ROC curve	0.622
Standard error a	0.0486
95% Confidence interval b	0.509-0.725
Significance level P (Area = 0.5)	.0124*
Youden index J	0.2431
Associated criterion	>13.9 µg/L
Sensitivity	38.89%
Specificity	85.42%
Accuracy	65.46%
Positive predictive value	66.7%
Negative predictive value	65.1%
Positive likelihood ratio	2.67
Negative likelihood ratio	0.72

*$P < .05$.
ª DeLong et al.; 1988 b Binomial exact

Table 3. ROC Analysis Summary for Serum ECP Using the Systemic Provocation Test as a Gold Standard for Diagnosis of Aspirin Intolerance and 11.3 µg/L as Cut-off Value

Area under the ROC curve (AUC)	0.601
Standard Error a	0.0532
95% Confidence interval b	0.488 to 0.706
Significance level P (Area = 0.5)	0.0584*
Youden index J	0.2014
Associated criterion	>11.3µg/l
Sensitivity	47.22%
Specificity	72.92%
Accuracy	61.9%
Positive predictive value	56.7%
Negative predictive value	64.8%
Positive likelihood ratio	1.74
Negative likelihood ratio	0.72

*$P > .05$.
ª DeLong et al.; 1988 b Binomial exact

Discussion

Early detection and efficient treatment of AI are essential to prevent disease progression, multiple revision surgeries, and complications in patients with CRS. Considering the limitations of the available *in vitro* and *in vivo* tests for AI and recent evidence and reports, there is still a need for a new, widely available, affordable, and cost-effective test that can enhance the early diagnosis of AI in patients with CRS.

A Chinese study done by Zheng et al.[23] showed that the ECP/myeloperoxidase (MPO) in nasal tissue had an acceptable discrimination value for predicting CRSwNP recurrence was a higher risk of AI in the recurrence group. This study did not address the discrimination value of serum ECP for the prediction of AI directly. Furthermore, measuring the ECP/MPO ratio in nasal tissue is an invasive procedure that requires a nasal tissue biopsy.

According to Benkler[10], AERD can be distinguished from CRSwNP by elevated eosinophil levels detected by ECP in the nasal tissue. In another study by Weidman[24], ECP in uncinate tissue was significantly higher in patients with AERD. These two studies showed a correlation between nasal ECP and AERD. If we consider that elevated serum ECP concentration is closely related

to higher eosinophil expression in nasal smears[19] and that nasal eosinophilia and nasal ECP are positively correlated,[25] we can assume a positive correlation between AERD and serum ECP indirectly. A study by Szczeklik[20] showed that serum ECP increased in patients with asthma and AI after ingestion of ASA. This was the only study that we found described the relationship between AI and serum ECP directly. However, the study group included patients with asthma and not CRS.

In this study, we analyzed and evaluated the serum ECP level as a cost-effective, readily available, non-invasive, and safe test in recognizing AI among patients with CRS (86%) mainly on the basis of the IV ASA challenge, the gold standard. All or at least most of the studies related to the diagnosis of AI were based on clinical history, FET[26] or oral challenge test.[16] This could explain the higher prevalence of AI among patients with CRS in our study (43%) compared with previous studies. According to Philpott et al.,[27] the prevalence of self-reported AI was 2.26% in the general population, 3.25% in CRSsNPs, 9.61% in CRSwNPs, and 40% in allergic fungal rhinosinusitis. However, the estimation of the prevalence of AERD varies according to the determinant: through a questionnaire (11-20%), medical record (~3%), and oral provocation test (21%).[28] We believe that the IV ASA provocation may detect more patients with AI than the oral provocation test and reduce false-negative results. The findings of Seong et al.[12] support this opinion; however, a trial on a larger scale should be undertaken to confirm these results.

Sensitivity and specificity are considered essential measures for the diagnostic accuracy of a given test, but they do not help estimate the probability of disease in a particular patient. By contrast, positive and negative predictive values provide estimates of disease likelihood in a particular patient. However, both parameters vary according to disease prevalence.[29] Therefore, knowing the actual prevalence is particularly important to interpret test results for an individual patient.

In our study, the percentage of women in the positive group (56%) was significantly higher than that in the negative group (12%) ($P < .0001$). This result is consistent with that mentioned in the literature.[30]

Interestingly, we also found that the percentage of those with nasal polyps was significantly higher in the negative provocation group than in the positive provocation group (40% vs. 11%, $P = .0034$). Similarly, the percentage of patients with bronchial asthma was higher in the negative provocation group than in the positive group (27% vs. 19%, $P = 0.4$). However, this difference was not statistically significant. These findings can be attributed to the high sensitivity and accuracy of the IV ASA challenge test. According to Seong et al.,[12] provocation test with IV lysine ASA was more efficacious than ASA oral challenge in the diagnosis of NSAID hypersensitivity (sensitivity 93.5%, specificity 100%, no false-positive cases, and three false-negative cases with single NSAID hypersensitivity, who did not react to the consecutive ASA oral challenge). Another point to mention here is that patients with recurrent CRS, even without nasal polyp or asthma, should be investigated for AI.

In our study, we noted a significant difference in the mean serum ECP level between the positive and negative provocation groups ($P = .0125$). Rasp et al.[25] and Di Lorenzo et al.[31] found no significant differences in the serum ECP levels of various CRS subtypes. However, they discussed serum ECP concerning the presence or absence of different types of allergic rhinitis or the presence or absence of nasal polyps. In both studies, AI was not discussed directly. Rasp et al. found elevated ECP levels in the nasal secretions of patients with all types of rhinitis without discrimination value for any particular nasal disease.

However, Di Lorenzo et al. have observed that ECP in nasal fluids from patients with nasal polyps was significantly higher than that observed in patients without nasal polyps. Again, these two studies did not address AI in particular. If we consider the fact that AI is a chronic systemic eosinophilic disease rather than a pure local inflammation, we can assume that serum ECP is a more specific marker for AI than the nasal ECP level in patients with CRS.

We identified the best cut-off value for serum ECP was >13.9 µg/L to determine whether the patient with CRS have AI. Although AUC of 0.62 was in the low category, we can still consider the serum ECP level as a useful diagnostic marker to detect patients with AI, especially if we consider the fact that the AUC has reached statistical significance ($P = .0124$) and that the interpretation of the significance of the AUC totally depends on the field in which it is applied. In clinical practice, this simple, readily available, and cost-effective test with 85.42% specificity, 65.46% accuracy, 66.7% PPV, and 2.67 PLR can be used to convince patients with CRS to undergo more accurate but uncomfortable, expensive, and not risk-free test. Elevated serum ECP levels can give the physician an indication about the possibility of AI ensuring NSAID is avoided as a painkiller during sinus surgery, or aspirin desensitization trial can be started in areas where the expensive and more accurate tests are not available or unaffordable.

Considering the limitations of the in vitro tests for AI, the provocation test is still the gold standard; however, it is usually restricted to confirm acute physical reactions of the body to ASA[17] and does not reflect the slow chronic body reaction to ASA as with CRS and polyp formation. In clinical practice, we see many patients with CRS whose provocation tests are negative but who show a significant response when undergoing trial therapy with ASA desensitization.

Absence of previous studies to compare our results with, the medium sample size, and the retrospective nature of data collection were our study's limitations. Regardless, to the best of our knowledge, this study is the first to evaluate the serum ECP level on the basis of IV ASA provocation to distinguish between patients who are ASA tolerant or intolerant. Standardization of the time for assaying the ECP level (especially when measuring the serum ECP and ingestion of cortisone, ASA, foods containing ASA or after sinus surgery, and removing inflammatory load) should be considered in future studies.

Conclusion

There is a high prevalence of AI in patients with CRS, which can be detected only by IV ASA challenge. The majority of patients with AI do not have nasal polyps or asthma. The mean serum ECP level in the positive ASA systemic provocation group is significantly higher than that in the negative group (19.3 µg/L and 8.6 µg/L, re-

spectively). Assaying serum ECP in patients with CRS could help diagnose AI, especially when other more accurate tests are not available. The best diagnostic cut-off value of serum ECP was 13.9 µg/L, and the corresponding specificity was 85.42%.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of the University of Ulm (approval number 423/20).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.R.A., N.Y.A., M.T., G.M.; Design - H.R.A., N.Y.A., G.M.; Supervision - M.T., G.M.; Resource - H.R.A., N.Y.A., M.T., G.M.; Materials - H.R.A., N.Y.A., M.T., G.M.; Data Collection and Processing - H.R.A., N.Y.A.; Analysis and Interpretation - H.R.A., N.Y.A., M.T., G.M.; Literature Search - H.R.A., N.Y.A.; Writing - H.R.A.; Critical Reviews - H.R.A., N.Y.A., M.T., G.M.

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