

Original Article

Uncovering key features for predicting comorbid chronic eosinophilic pneumonia in chronic rhinosinusitis via machine learning

Running title: Clinical features of CRS with CEP

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35 Ethics declarations

36 The Research Ethics Committee of Amagasaki Medical Center approved the study protocol
37 (approval no. 2-211). All the experiments were performed in accordance with the principles of
38 the Declaration of Helsinki.

39

40 Previous presentation

41 This research, the manuscript, and the abstract have not been presented previously.

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Abstract

Background: Chronic eosinophilic pneumonia (CEP) can occur concurrently with chronic rhinosinusitis (CRS). However, crucial features of comorbid CEP in patients with CRS remain unclear.

Methods: Features of comorbid CEP were thoroughly investigated using machine learning (ML). In ML, (i) highly predictable performance and (ii) high interpretability (e.g., presenting classification rules understandable to clinicians) are two objectives with a tradeoff relationship, resulting in both being simultaneously unachievable by a single ML model. In this study, for (i), ML models were examined to check their predictive performance, and for (ii) decision tree (DT) was used. In addition, to address the lack of interpretability in (i), SHapley Additive exPlanations (SHAP) was applied.

Results: In total, 372 CRS samples (21 with CEP) were collected. In the CRS with CEP group, 19 patients were diagnosed with eosinophilic CRS (ECRS). In (i), extreme gradient boosting (XGBoost)/random forest (RF) showed a higher AUC (Area Under the ROC (Receiver Operating Characteristic) Curve) than logistic regression/support vector machine. In (ii), the top feature was a blood eosinophil count $\geq 1446/\mu\text{L}$, followed by a white blood cell (WBC) $\geq 9.25 \times 10^3/\mu\text{L}$, and C-reactive protein (CRP) $\geq 0.335 \text{ mg/dL}$. SHAP, based on XGBoost and RF, selected elevations in the blood eosinophil count, CRP, and WBC count as the top three features.

Conclusion: DT and SHAP selected the same three top features of CRS with CEP. When patients with CRS satisfy the DT algorithm, they may have ECRS with CEP. Therefore, otolaryngologists should perform sinonasal biopsies and chest imaging.

68 Introduction

69 Chronic eosinophilic pneumonia (CEP) is an idiopathic pulmonary disease with eosinophil-related
70 inflammation ¹, with an incidence of 0-2.7% among interstitial lung diseases ². Patients suffer from
71 prolonged respiratory symptoms, such as cough (60–90%) and shortness of breath/dyspnea (20–
72 50%). Patients with CEP respond well to corticosteroid (CS) treatment; however, relapse
73 frequently occurs during tapering of the CS dose or after cessation of treatment. The pathogenesis
74 remains unclear; however, some studies have reported an increase in type 2-related cytokines,
75 such as IL-5, IL-13, and IL-25, in the bronchoalveolar lavage (BAL) fluids ³⁻⁵. Increased type 2-
76 related cytokines are associated with increased eosinophils ⁶. Based on this background, recent
77 reviews reported the efficacy of biologics, especially the ones related to IL-5, on the management
78 of CEP ^{7,8}. The comorbidities observed at the onset of CEP include atopy, asthma, allergic rhinitis,
79 and chronic rhinosinusitis (CRS). In comorbid CRS, approximately 10% of patients with CEP
80 present with nasal polyps (NPs) ^{9,10}, which are one of the representative features of CRS ¹¹. A
81 previous study investigated the detailed phenotypes of 10 patients with CRS and CEP ¹². When
82 patients with a blood eosinophil count of $\geq 500/\mu\text{L}$ visited pulmonologists for pneumonia, the
83 pulmonologists consulted otolaryngologists for potential comorbid CRS prior to CS treatment.
84 When sinonasal computed tomography (CT) revealed comorbid CRS, otolaryngologists and
85 pulmonologists performed the following procedures under general anesthesia: endoscopic sinus
86 surgery (ESS) for the investigation of CRS phenotypes and treatment and BAL for CEP diagnosis.
87 As a result, eosinophilic CRS (ECRS) with blood eosinophil count $\geq 1,500/\mu\text{L}$ was observed in
88 90% of CEP patients, indicating that eosinophilic inflammation can simultaneously occur in the
89 sinonasal tissues, lungs, and blood.

90 ECRS and CRS with NPs (CRSwNPs) are defined as type 2 cytokine-related CRS ¹¹. They have
91 a higher rate of postoperative recurrence ^{13,14} and worsened postoperative symptoms ¹⁵ in
92 comparison to those with non-type 2 CRS. Some biologics targeting not only IL-5 but also IL-4/IL-

13 can be effective for the type 2 cytokine-related CRS ^{11,16}. However, it remains unclear which of biologics can be appropriate for the management of CRS with CEP. The exploration of the endotypic features using sinonasal samples might contribute to appropriate biologics selection for CRS with CEP. However, it is difficult to collect the sinonasal samples for the following reasons: The department of respiratory medicine is the first consultation sector for CEP in general. Therefore, otolaryngologists have few opportunities to consult with CEP patients when having no collaboration with pulmonologists. In addition, otolaryngologists have few information implying potential comorbid CEP among CRS patients, and have less motivation to perform chest imaging tests such as CT for CRS diagnosis. The clarification of distinct features in CRS with CEP might motivate otolaryngologists to perform chest imaging tests, increasing the frequency of detecting comorbid CEP. As a result, studies investigating the endotype in CRS with CEP might be conducted, leading to the appropriate selection of biologics.

The concept of machine learning (ML), at the heart of modern artificial intelligence (AI), involves training a model that represents the underlying rules in given data using an objective-specific algorithm ¹⁷. ML methods are widely used for disease diagnosis and outcome prediction in the medical field. Compared with conventional (simple) statistical methods, ML methods can provide better predictive ability for diagnosis and outcomes owing to richer model representation ^{18,19}. In addition, the purpose of ML is different from that of conventional statistical methods ²⁰ in the sense that conventional methods attempt to understand the relationships between clinical features, whereas ML methods pursue 1) achieving better predictive performance (prediction accuracy) and 2) presenting classification rules that are understandable to clinicians (interpretability) ²¹. However, high prediction accuracy and interpretability have a tradeoff relationship, making it difficult to generate a model with both abilities ²¹. Simple ML models with a small number of parameters in an understandable formulation can be interpreted easily; however, their representational power and predictive performance are limited. However, ML models with rich

predictive performance are usually complex and sometimes even a so-called black box, giving only a large number of parameter values that are difficult to summarize and understand, resulting in less interpretability²¹. For instance, two representative (supervised) ML methods are decision tree (DT) and random forest (RF)²². A DT, a classification tree with decision and leaf nodes, provides a tree-structured flowchart in which the decision-making process is visualized by repeatedly dividing the training data using the most decisive feature value at each decision node. The visible flowchart makes the DT highly interpretable with a moderate predictive performance. To enhance the predictive performance of DT, RF generates multiple DTs, that is, a more complex model, by training each DT on a different distribution of training data generated by random sampling from the original training data. Consequently, RF can achieve a higher predictability than DT, but the resulting multiple decision trees are difficult to summarize and interpret. To extract the key features from such complex models, SHapley Additive exPlanations (SHAP) is developed and utilized as a typical technique for explainable AI²¹.

This study aimed to investigate the clinical features of comorbid CEP in patients with CRS by using ML. Because of the trade-off in ML between predictive performance and interpretability, we adopted two separate approaches: 1) predictive performance: four ML models were compared to examine the classification ability and determine the best predictive models, and 2) interpretability: DT, which can provide a visual tree-structured decision flowchart, was used. Additionally, SHAP was applied to the predictive models identified in Step 1), to extract the key and decisive features for predicting comorbid CEP in patients with CRS.

Materials and methods

Data collection and preprocessing of data

The Research Ethics Committee approved the study protocol (approval no. 2-211). All the experiments were performed in accordance with the principles of the Declaration of Helsinki. All data were retrospectively collected from the medical records. The opt-out method was used to obtain informed consent.

Data were obtained from patients with CRS aged ≥ 18 years who underwent ESS between April 2018 and September 2024. For the diagnosis of CRS with CEP, collaboration between otolaryngologists and pulmonologists was established as described above. CEP was diagnosed by pulmonologists based on clinical symptoms lasting two weeks, inflammation on chest CT, and/or eosinophilia detected in BAL ($> 25\%$)¹². Acute eosinophilic pneumonia and CEP share some similarities; however, a distinct feature in the former is the occurrence of severe acute respiratory failure threatening life¹. In our study, as none of the patients showed severe acute symptoms, all patients were considered to have CEP. The exclusion criteria were the presence of other known eosinophilic pneumonias, such as allergic bronchopulmonary aspergillosis and parasitic infections, eosinophilic granulomatosis with polyangiitis (EGPA), and biologics-related CEP. For the differential diagnosis of these diseases, blood markers (e.g., *Aspergillus*-/parasite-specific IgE and anti-neutrophil cytoplasmic antibodies) were measured. CRS was diagnosed by otolaryngologists based on the clinical symptoms and sinonasal CT findings. Radiologists evaluated sinonasal and chest CT findings and identified CRS/CEP. The exclusion criteria for CRS were history of malignancy, long-term oral CS treatment (> 1 month), and use of biologics for systemic inflammatory diseases, antrochoanal polyps, cystic fibrosis, fungal sinusitis, or acute sinusitis. In CRS without CEP, chest imaging studies are not usually performed to assess lung status. Therefore, it is difficult to exclude the possibility of lung inflammation in patients with CRS without CEP. To minimize this potential as much as possible, patients with CRS who underwent ESS were selected because they underwent blood tests and chest radiography on the same day as the preoperative examinations. When pulmonologists did not find any inflammatory findings

specific for CEP on chest radiography, the patients were considered to have CRS without CEP. Blood data collected during preoperative examinations were analyzed. All patients underwent ESS within one month of the preoperative examination, and the eosinophil count data in the sinonasal tissues were used for ESS. In one patient with CRS without CEP, CEP onset was observed during the follow-up period. In one patient with CRS and CEP, CEP relapse was observed during the follow-up period. These were regarded as additional data.

The following features were collected: patients' background information, such as age, sex, body mass index (BMI), smoking history, smoking index (Brinkman index), and the past history of ESS; the presence of comorbid asthma, aspirin intolerance, non-steroidal anti-inflammatory drugs (NSAIDs) allergy, allergic rhinitis, atopic dermatosis, food allergy, drug allergy, inhaled CS (ICS) status/dosing categories, and prednisolone equivalents based on ICS potency and adherence; endoscopic findings of NP, NP score²³, disease location (bi- or hemi-lateral CRS), the presence of eosinophils in rhinorrhea, and eosinophil count in sinonasal tissues; subjective symptoms using the total score of the 22-Item Sino-Nasal Outcome Test (SNOT-22)²⁴, visual analogue scale (VAS) ranging from 0 to 3 for rhinorrhea, one for nasal obstruction, one for olfaction; Lund-Mackay CT scores²⁵; blood test results, including the white blood cell (WBC) count, C-reactive protein (CRP) and total IgE levels, Neutrophil/Lymphocyte ratio (NLR), actual values and percentages of neutrophils, lymphocytes, eosinophils, basophils and monocytes, and class of allergen-specific IgE to 13 allergens. For these features, the binary variables were sex, smoking history, past history of ESS, presence of comorbidities, presence of NP, disease location, and presence of eosinophils in rhinorrhea. Ordinal variables included smoking history, ICS status/dosing categories, VAS scores reflecting symptoms, and the class of IgE specific to allergens in blood tests. The other features were defined as continuous variables. For histopathological analyses, the NPs in CRSwNPs and the mucosa of the ethmoid cavity in CRS without NPs (CRSsNPs) were used²⁶. The eosinophil count in the sinonasal tissues was calculated using high-power field

(HPF) microscopy in the three densest areas of each slice (magnification $\times 400$), and the average count was used for analysis²⁶. ECRS was defined as the averaged eosinophil count in sinonasal tissues $\geq 10/\text{HPF}$ ¹¹. Patients with a blood eosinophil count $\geq 500/\mu\text{L}$ were regarded as having eosinophilia²⁷. The severity of eosinophilia was subdivided into mild ($\geq 1000/\mu\text{L}$ and $< 1500/\mu\text{L}$), moderate ($\geq 1500/\mu\text{L}$ and $< 5000/\mu\text{L}$), and severe eosinophilia ($\geq 5000/\mu\text{L}$)²⁸. All comorbidities except allergic rhinitis were assessed using a questionnaire, and allergic rhinitis was diagnosed according to previously published guidelines²⁹. The Lund-Mackay CT scores in each of the six regions ranged from 0 to 4. The total score was assessed bilaterally and ranged from 0 to 24 points. The severity of sinonasal CT findings was divided into the mild (1-4), moderate (5-10), and severe (11-24) groups³⁰. There are several clinically available ICS molecules, and their potential (relative glucocorticoid receptor binding affinity) and regimens (e.g., single or double inhalation per day) differ. ICS molecules with higher potency require a lower dose to occupy the same number of receptors in the airway, contributing to a lower daily dose for equivalent efficacy³¹. In the ICS dosing categories, four classes were established based on the Global Initiative for Asthma Strategy: none, low, medium, and high doses³². This classification is based on a simple dose equivalence approach, in which potency is ignored. In the current study, some patients' adherence to the management of CRS without CEP was poor, regardless of the clinicians' instructions for daily ICS therapy for asthma control. For the ICS status, three classes were established depending on frequency: non-, as-needed-, and daily users. As-needed users were assumed to receive ICS treatment 3-4 times per week. Even under the same regimen, as-needed users are known to receive total ICS dosages less than daily-users³³. Thus, the simple dose-equivalence approach might cause a bias. To address this issue, we referred to the methodology of converting total doses of ICS into a prednisolone equivalent dose representing the systemic exposure based on the effects of ICS potency and adherence for 28 days³³. Three types of ICS (budesonide, fluticasone propionate, and fluticasone furoate) and two regimens of ICS frequency (daily and as-

needed users) were set. None of the patients were administered any other ICS molecules. The total ICS dose per day was calculated based on the methodology described above and converted into prednisolone equivalent dose per day (Supplementary table 1). Among all the variables, the overall rate of missing data was less than 0.83%. Missing data were inputted as average values or modes for the variables.

Machine learning (ML): Models and experimental settings

Owing to the two distinctive objectives of ML, that is, high predictive performance and high interpretability, we adopted two approaches: 1) For predictive performance, the obtained data were divided into training and test data under 10-fold cross-validation. The performance result (we used the area under the receiver operating characteristic (ROC) curve (AUC), see below) was averaged over the 10 folds, in each of which the AUC was computed for the test data using the model trained by the training data. Four representative ML models were prepared: RF, eXtreme Gradient Boosting (XGBoost), logistic regression (LR), and support vector machine (SVM). For each method, in each of the 10 folds, hyperparameters were tuned by inner 10-fold cross-validation (training data were further divided into training and evaluation data, where the evaluation data were used to find the optimal hyperparameters). Considering the imbalanceness in our data (only 21 cases with CEP out of all 372 CRS cases), cost-sensitive learning (CSL) and Synthetic Minority Oversampling Technique (SMOTE) were applied to avoid a situation in which the minor class (CRS with CEP) was ignored in training the ML models³⁴. For interpretability, DT was applied to all samples to obtain a visible tree-structured, understandable diagnostic rule for clinicians. Finally, SHAP was applied to the predictive models in Step 1 to examine the features important for distinguishing CRS with CEP from CRS³⁵.

Four ML models: Linearity/nonlinearity and the reasons why these four are selected

DT is an algorithm that repeats the data-partition step. This step involves choosing a feature, that is, the best feature regarding a criterion for classification, such as information gain, resulting in dividing examples that are most relevant to the classification (dependent variable) labels. The DT is a linear classification model. The RF runs the DT algorithm several times, each with a different random sampling of features and examples. As a result, RF generates multiple DTs and combines them for prediction, resulting in nonlinearity, regardless of the linearity of DT. Similar to DT, XGBoost repeats the step of choosing a feature, whereas the example distribution changes depending on the steps, resulting in the non-linearity of XGBoost. In contrast, LR estimates the weights over the features, which means that the model is linear. Although the SVM formulation is a linear function, this linear function is over a space called the kernel space, to which the original examples are projected in a nonlinear manner, resulting in the non-linearity of SVM for classification (In our experiments, we used a Radial basis function (RBF) kernel, which also can incorporate the non-linearity into SVM). Four methods (RF, XGBoost, LR, and SVM) were selected for classification performance validation in our work based on the following two points: 1) the method is well used and 2) the method is appropriate for medium- or small-sized datasets, like our dataset. Although widely used these days, deep learning requires big data, which is far larger than our dataset; therefore, we did not use deep learning.

Statistical analyses

Quantitative variables were presented as medians with interquartile ranges and means with standard deviations. The Mann-Whitney U test and Fisher's exact test were used for continuous and binary/ordinal variables, respectively. Statistical significance was set at $p < 0.01$. For the sample size calculation, a power of 80 or 90%, a 2-sided alpha level of 1%, and a standard

deviation common to two groups were set for the analyses. R software (version 3.6.1; R Foundation for Statistical Computing) was used for the univariate analyses.

The AUC values under the ROC curve based on the test data were used to evaluate the predictive performance of the ML models. Paired t-tests were used to investigate the differences in mean AUC values between the models. Python software version 3.6.6 (Python Software Foundation, Wilmington, DE, USA) was used to implement the ML models.

Results

Frequency and phenotypes of comorbid CRS in patients with CEP

In total, 23 patients with CEP visited otolaryngologists, of whom 21 (91%) had comorbid CRS. Patients with comorbid CRS were subdivided based on their phenotypes and presence of moderate/severe eosinophilia (Supplementary figure 1). Nineteen (82%) patients were diagnosed with ECRS, of whom nine (39%) had eosinophilic CRSsNPs (ECRSsNPs). Fifteen (65%) patients were diagnosed with CRS and moderate/severe eosinophilia, of which 13 (57%) had ECRS. Representative endoscopic nasal and imaging findings of ECRSsNPs with CEP are shown in Figure 1.

Comparison between CRS without and with CEP in univariate analyses

In total, 351 and 21 data points were collected for the CRS without and with CEP, respectively. Comparisons of patient backgrounds, comorbidities, endoscopic and histological findings, and subjective symptom scores between patients with CRS with and without CEP, based on univariate analyses, are shown in Table 1. Univariate analyses revealed some distinct features of CRS with CEP, including a lower BMI and higher frequency of ECRSsNPs. There was a significant

difference in prednisolone equivalent doses based on ICS potency and adherence; both median values were zero, but the third quartile was higher in patients with CRS with CEP. The total Lund-Mackay CT score was significantly lower in the CRS with CEP group (Supplementary figure 2a). When comparing the scores of each sinus region, lower CT scores were observed in the maxillary and frontal sinuses in the CRS with CEP group (Supplementary figure 2b). Four patients with CRS with CEP showed a score ≥ 18 , while the others had a score ≤ 6 (Supplementary figure 2a). After subdividing the patients with CRS with CEP into mild, moderate, and severe groups based on the CT findings, the score difference was assessed for each sinus region (Supplementary figure 2c). The mild and moderate groups showed lower scores in all sinus regions, and the anterior and posterior ethmoid sinuses were common regions of inflammation in both groups. In blood tests, the CRS with CEP group showed higher WBC, CRP, IgE, and monocyte counts, higher eosinophil percentage and count, lower percentages of neutrophils and lymphocytes (Figure 2a-h and Supplementary table 2), and a higher class of IgE specific to two allergens (epithelium and *Staphylococcus aureus* enterotoxin A; Supplementary table 3). The total of 6 (29%), 8 (38%), and 7(33%) patients showed mild, moderate, and severe eosinophilia, respectively (Figure 2h).

Machine learning: 1) for predictive performance

The mean AUC values of the four ML models (Figure 3a) revealed that 1) XGBoost achieved the highest AUC value (0.966 ± 0.138), followed by RF (0.957 ± 0.119), while 2) LR (0.937 ± 0.121) and SVM (0.942 ± 0.126) exhibited lower values than RF and XGBoost. These results suggest that 1) the uniformly high AUC values across models imply robust predictive performance, and 2) the superior performance of RF and XGBoost may be due to their ensemble nature, that is, generating multiple DTs, which provides greater complex and representation power compared to single models like LR and SVM. This implies that the results (Figure 3a) are consistent with the

complexity of the models. However, the differences in AUC values between models were not statistically significant (Figure 3b). Supplementary figure 3 presents the mean AUC of the four ML methods using CSL and SMOTE. Because the original XGBoost achieved a high AUC value of 0.966, CSL and SMOTE did not improve the AUC further; RF with CSL and XGBoost with SMOTE achieved AUCs of 0.974 and 0.961, respectively (Supplementary figure 3a). In both the CSL and SMOTE, there were no significant differences in the mean AUC values between models (Supplementary figure 3b).

Machine learning: 2) for interpretability

Figure 4 shows the results of DT. The classification (decision) tree first divided patients with CRS into two subsets based on a blood eosinophil count threshold of $1446/\mu\text{L}$, that is, a patient with a blood eosinophil count not larger than 1446 (true) went to the left and was categorized into the non-CEP class; otherwise, the patient went to the right. At the next decisive node on the right, the patient with a WBC count of less than $9.25 \times 10^3 / \mu\text{L}$ went to the left, again being categorized into the non-CEP class; otherwise the patient went to the right again for one further examination. Patients with a CRP level $< 0.335 \text{ mg/dL}$ went to the left, being categorized into the non-CEP class; otherwise, patients went to the right into the CEP class. This DT was trained using all 372 samples, and achieved an AUC of 0.922, which was sufficient for detecting CEP in CRS. Note that this was not obtained using cross-validation, since the primary objective of this step was high interpretability rather than high predictability.

Sorting features by SHAP with random forest

The results of applying the SHAP to the original XGBoost (AUC value: 0.966) obtained in step 1) to sort features in terms of the importance of CRS with CEP are presented as a beeswarm plot (Figure 5). This plot indicates that the top three features were obtained from the blood tests. The most crucial feature of CRS with CEP was “increased blood eosinophil count,” followed by

“Increased CRP,” and “increased WBC.” On applying SHAP in RF with CSL (AUC value: 0.974), increases in the blood eosinophil count, CRP, and WBC were the top three features, i.e., same as the features selected by the original XGBoost (Supplementary figure 4).

Sample size calculation for top ten features

For the sample size calculation, the top ten features in the original XGBoost were selected (Supplementary table 4). The number of patients was statistically sufficient for all features except the NLR.

Discussion

This study revealed the key clinical features for detecting comorbid CEP in patients with CRS using two ML approaches: high predictive performance and interpretability. In the first approach, high AUC values were observed for RF and XGBoost, regardless of the presence or absence of CSL or SMOTE. In the second approach, DT presented the algorithm using three features with the following cutoff values: a blood eosinophil count of 1446/ μ L, WBC count of 9.25×10^3 / μ L, and CRP level of 0.335 mg/dL. SHAP selected an increase in blood eosinophil count, WBC count, and CRP level as the top three features, consistent with the results of DT.

The first approach showed the possibility of highly precise prediction (diagnosis) using high AUC values but suffered from a lack of interpretability, whereas the second approach provided a visible, understandable procedure for diagnosing CRS with CEP. The application of SHAP helped us determine which features were crucial for CRS with CEP; however, SHAP remained at the single-feature (univariate) level and did not provide any concrete numbers, such as cutoff values, for the crucial features. All in all, the combination of all these three results demonstrated the possibility of building a highly precise diagnosis procedure, in which the key, crucial feature

would be the blood eosinophil count with a cutoff value of 1446/ μ L. These results indicate the importance of performing blood tests to detect comorbid CEP.

In this study, the data were imbalanced. Therefore, we investigated whether the application of two typical ML techniques for imbalanced data, CSL and SMOTE, affected the results. Although the AUC value of RF with CSL was slightly higher than that of the original XGBoost, the top three features for CRS with CEP, as shown in SHAP, were the same as those of DT, regardless of dealing with imbalances. The main aim of this study was to extract the key and decisive features of CRS with CEP rather than to establish ML models with the best predictive performance. Therefore, we showed the results of SHAP obtained from the original XGBoost and RF with CSL, and confirmed that the top three features can be decisive for CRS with CEP.

Blood eosinophil count was selected as a more crucial feature than blood eosinophil percentage and eosinophilic count in the sinonasal tissues. In patients with CRS without CEP, the number of those with ECRS was 254 (72%), and the average eosinophil count in sinonasal tissues was 83/HPF. The relatively high eosinophil count in the sinonasal tissues in patients with CRS without CEP can be attributed to the higher proportion of ECRS. Selection bias might be a plausible reason why the blood eosinophil count outperformed the histological count. Our findings highlight the importance of checking the blood eosinophil counts by clinicians. An increased blood eosinophil count (eosinophilia) can occur in several diseases, including allergic diseases, malignancies, drug reactions, parasitic diseases, and atopic diseases ³⁶. In this study, fifteen patients with CRS with CEP had moderate/severe eosinophilia, of whom seven had severe one (Figure 2h). Hypereosinophilic syndrome (HES) is a rare disorder without a known cause that is characterized by blood/tissue eosinophilia ³⁷. The definition and diagnostic criteria of HES consist of the following: blood eosinophil count $\geq$ 1500/ μ L on two examinations at least 2 weeks apart (hypereosinophilia); tissue eosinophilia-driven organ damage and/or dysfunction;

and exclusion of other disorders causing organ damage³⁸. When patients with CEP, CRS, and moderate/severe eosinophilia are diagnosed with ECRS, they might be regarded as having HES with eosinophilia-driven damage in the sinonasal and pulmonary sites. Secondary (reactive) HES is one of HES variants, and its underlining mechanism can be due to the cytokine-driven hypereosinophilia³⁸. At present, the patients with EGPA is categorized into the secondary HES. Patients with ECRS with CEP and moderate/severe eosinophilia might be classified into the secondary HES.

In CRS with CEP, approximately 40% of patients have ECRSsNPs. In the SHAP model, the presence of NP did not rank within the top 20 crucial features. The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 defines CRSwNPs and ECRS as type 2-related cytokine CRS¹¹. Clinical studies focusing on the relationship between CRSwNPs and ECRS are widespread, while those focusing on the relationship between CRSsNPs and ECRS are less frequent^{39,40}. The endotype of CRS consists of type1, 2, and 3, and their mixed patterns, independent of the existence of NPs¹⁶. Under certain conditions, CRSsNPs can be diagnosed as ECRS. A previous study developed predictive models for eosinophil counts in sinonasal tissues using three features and revealed the conditions for the diagnosis of ECRSsNPs⁴¹. When assuming CRSsNPs with a blood eosinophil count $\geq 1500/\mu\text{L}$, the model predicted that the average eosinophil count in sinonasal tissues can be likely $\geq 10/\text{HPF}$ regardless of asthma status. There is no consensus regarding the cut-off values for eosinophilic counts in sinonasal tissues for ECRS diagnosis, and their values range from 5 to 350/HPF⁴². When defining the eosinophilic count in sinonasal tissues $\geq 10/\text{HPF}$ as ECRS, CRSsNPs with moderate/severe eosinophilia may potentially be ECRS.

The sinonasal CT findings in the CRS with CEP group were interesting. One recent study used the Lund-Mackay CT score and compared sinonasal CT findings between patients with CRS

with and without EGPA³⁰. Patients with EGPA had lower total scores than those with NSAID-exacerbated respiratory diseases or ECRS without asthma. In addition, there was large variability in the total scores. When patients with EGPA were subdivided into three groups according to score differences, the main inflammation in the mild/moderate group occurred in the maxillary and anterior ethmoid sinuses, and that in the severe group occurred in the ostiomeatal complex. The mild/moderate group showed a poor prognosis, such as cardiac involvement. EGPA progresses through a prodromal phase, an eosinophilia-driven phase, and vasculitis phase⁴³. CRS and CEP are observed in the prodromal and eosinophilia-driven phases, respectively. In this study, the CRS with CEP group showed lower total scores and large variability in the total scores, similar to the EGPA findings. As the mild/moderate CRS with CEP group might imply a poor prognosis (e.g., progression to EGPA), a longitudinal follow-up term should be determined.

Our current study has the following limitations. First, it was designed as a retrospective study at a single institution. Institutional bias owing to the small sample size may have affected the results. Cross-validation was used to reduce bias and examine the general predictive performance of the ML algorithms. In addition, a sample size calculation was performed on the top ten features of the original XGBoost. As a result, the numbers for each group were sufficient for all features except the NLR. Second, chest radiography and CT were used to assess lung status in patients with CRS with and without CEP, respectively. Therefore, when the level of lung inflammation is unremarkable on radiography, the presence of comorbid CEP may be underestimated in patients with CRS without CEP. To minimize this potential, the radiographic findings were evaluated by a pulmonologist. Third, the predictive ability of the ML techniques should be validated in future studies. In the process of revealing crucial features of CRS with CEP, our current study was unable to prepare validation data because CEP is a rare disease, which limited the sample size for CRS with CEP. Therefore, the predictive ability due to the

441 trained models in our current study may possess the overfitting. For validation, designing
442 multicenter-studies would be important.

443

444 In conclusion, ML methods were helpful in revealing increases in blood eosinophil count
445 (moderate/severe eosinophilia), WBC count, and CRP level as the top three features of CRS
446 with CEP. When patients with CRS satisfy the algorithm shown in the DT, ones may have ECRS
447 with CEP. In such cases, otolaryngologists should perform sinonasal biopsy and chest imaging.
448 A future multi-center study design with a collaboration between otolaryngologists and
449 pulmonologists is needed to validate the predictive ability obtained in this study.

450

Author contributions

M. I. was responsible for the conceptualization, manuscript drafting, study design, and manuscript revision. Z. J. and C. H. N. performed machine learning analyses. H.H. contributed to surgical procedures. S.T., K.E., T. H., H. M., E. S., and K. O. contributed to data collection and radiographic checks. H. M. drafted the manuscript and performed machine learning analyses. All authors read and approved the final version of the manuscript for submission.

Data availability statement

Data supporting the findings of this study are available upon request from the corresponding authors.

Ethics declarations

The Research Ethics Committee of Amagasaki Medical Center approved the study protocol (approval no. 2-211). All the experiments were performed in accordance with the principles of the Declaration of Helsinki.

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Figure legends

Figure 1. Representative X-ray, CT, and endoscopic findings. A 39-year-old female patient diagnosed with ECRSsNPs with CEP. **(a)**: Chest X-ray reveals consolidation in the left lung. **(b)**: Chest CT reveals inflammation with bronchodilation in the left lung. **(c and d)**: The bilateral absence of NPs is observed endoscopically. **(e and f)** Minor inflammation is observed in the anterior and posterior ethmoid sinuses. Abbreviations: CEP, Chronic eosinophilic pneumonia; CT, Computed tomography; ECRSsNPs, Eosinophilic chronic sinusitis without nasal polyps; IT, Inferior turbinate; MT, Middle turbinate; NS, Nasal septal; UP, Uncinate process.

Figure 2. Comparison of data obtained from blood tests between CRS without and with CEP. **a**, White blood cell; **b**, CRP; **c**, IgE; **d**, Blood neutrophil percentage; **e**, Blood lymphocyte percentage; **f**, Blood monocyte count; **g**, Blood eosinophil percentage; **h**, Blood eosinophil count. Data are presented as medians. Mann-Whitney U tests are applied. A significant p -value is set at < 0.01 . In **(h)**, the dotted lines indicate a blood eosinophils count of 1500 and 5000/ μ L. Abbreviations: CEP, Chronic eosinophilic pneumonia; CRP, C-reactive protein.; CRS, Chronic rhinosinusitis.

Figure 3. Comparison of ROC curves and AUC values among original four ML models. **(a)** Comparison of ROC curves among four original ML models. **(b)** Statistical comparison of the AUCs among the four ML models. Paired t-tests are applied. A significant p -value is set at < 0.01 .

Abbreviations: AUC, Area under the curve; CSL, LR, Logistic regression; ML, Machine learning; RF, Random forest; ROC, Receiver Operating Characteristic; SD, standard deviation; SVM, Support vector machine; XGBoost, extreme Gradient Boosting.

650

651 **Figure 4. DT to detect comorbid CEP in CRS patients.** Three features (along with their cut-off
652 values) are used in the DT.

653 Abbreviations: CEP, Chronic eosinophilic pneumonia; CRP, C-reactive protein; CRS, Chronic
654 rhinosinusitis; DT, decision tree.

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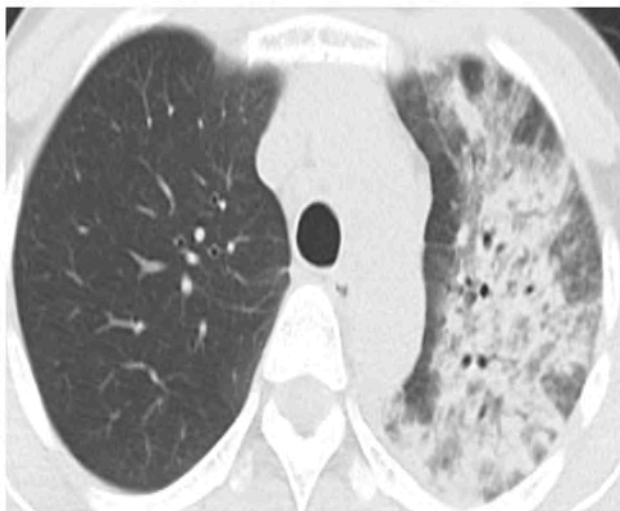
656 **Figure 5. The SHAP beeswarm plot using the original XGBoost.** Features derived from
657 blood tests are shown in yellow boxes.

658 Abbreviations: BMI, Body mass index; CRP, C-reactive protein; CT, Computed tomography;
659 ICS, Inhaled corticosteroid; NLR, Neutrophil/Lymphocyte ratio; NP, Nasal polyp; SHAP, SHapley
660 Additive expansion; SNOT; Sinonasal outcome test; VAS, Visual analog scale; WBC, White
661 blood cell; XGBoost, extreme Gradient Boosting.

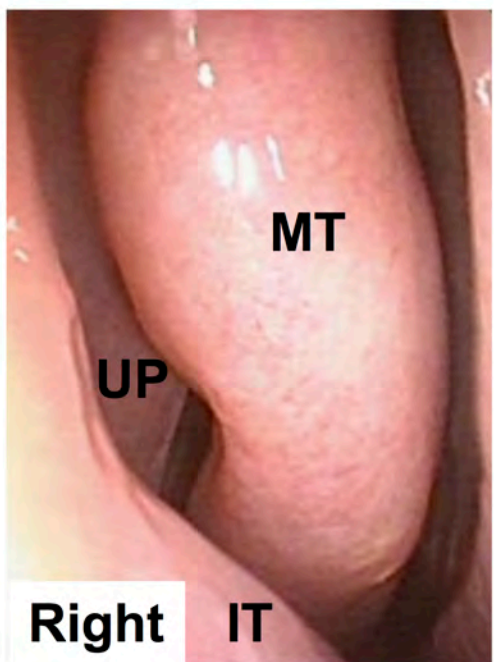
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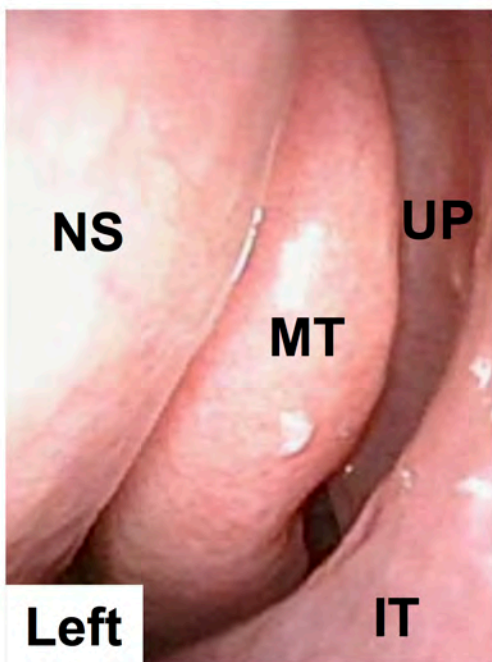
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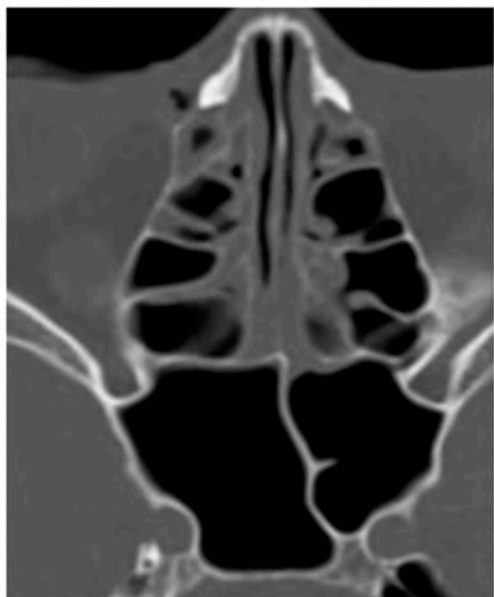
(c)



(d)



(e)



(f)



1 **Tables**

Table 1. Comparison of backgrounds, comorbidities, endoscopic and histological findings, and score of subjective symptoms between both groups

			Without CEP N = 351	With CEP N = 21	p-value
Patients' backgrounds	Age		61 (48, 71)	49 (40, 62)	0.01
	Male (n)		204	10	0.37
	BMI		23.3 (20.9, 25.7)	21.3 (18.3, 23.7)	< 0.01
	Smoking history (n)	None	169	12	0.19
		Past	136	9	
		Current	46	0	
Comorbidity	Smoking index		20 (0, 400)	0 (0, 220)	0.34
	Past history of ESS (n)		150	3	0.01
	Asthma (n)		120	12	0.06
	ICS status (n)	Non-user	259	12	0.22
		As-needed-user	5	0	
		Daily user	87	9	
	ICS dosing categories (n)	Non-user	259	12	0.01
		Low	29	0	
		Medium	38	3	
		High	25	6	
	Prednisolone equivalent dose based on ICS potency and adherence (mg/day)		0 (0, 0.13)	0 (0, 0.58)	< 0.01
	Aspirin intolerance (n)		13	0	1.00
	NSAIDs allergy (n)		4	0	1.00
	Eosinophil otitis media (n)		7	0	1.00
	Allergic rhinitis (n)		230	17	0.16
	Atopic dermatitis (n)		8	0	1.00
	Food allergy (n)		13	1	0.56
	Drug allergy (n)		33	1	0.71
Endoscopic and histological findings	CRSwNP (n)		257	10	0.02
	CRSSNP (n)		94	11	
	NP score		2 (0, 4)	0 (0, 2)	0.01
	Bilateral CRS (n)		297	19	0.75
	Presence of eosinophil in rhinorrhea (n)		241	17	0.33
	Eosinophil count in sinonasal tissues		83 (7, 170)	113 (70, 243)	0.04
	ECRS *		254	19	0.08
	ECRSsNPs (n)		29	9	< 0.01
Score for subjective symptoms	SNOT-22 total score		31 (18, 52)	31 (21, 42)	0.94
		0	42	2	0.48
	VAS for rhinorrhea	1	81	2	
		2	140	11	
		3	88	6	
		0	67	4	0.65

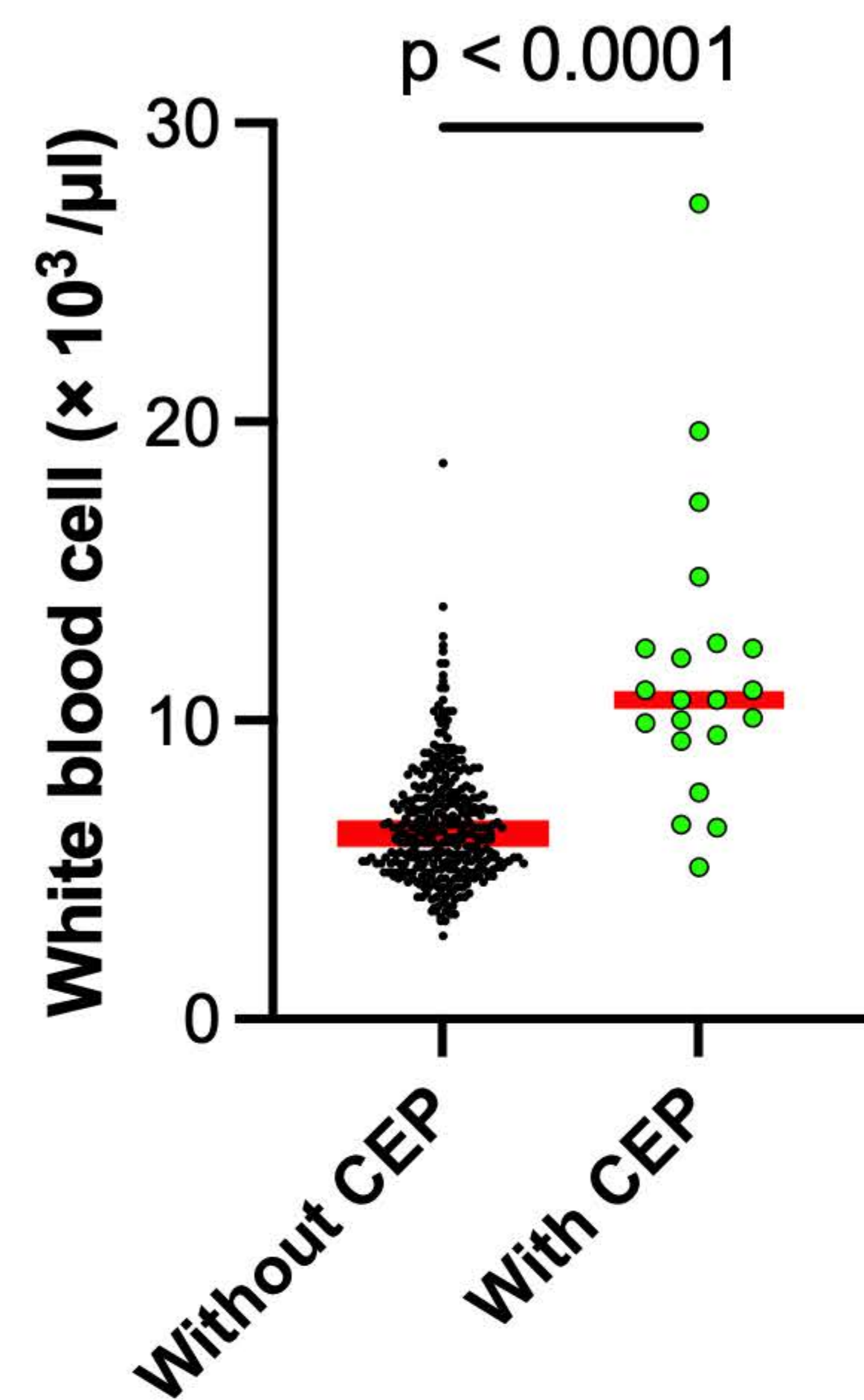
VAS for	1	118	7	
nasal	2	81	7	
obstruction	3	85	3	
	0	91	9	
VAS for	1	60	2	
olfaction	2	58	5	0.19
	3	142	5	

* The eosinophil count in sinonasal tissues ≥ 10 /HPF is defined as ECRS. Data for continuous variables are present with median (IQR). Fisher's exact tests are used for ordinal and binary variables, while Mann-Whitney U tests for continuous variables.

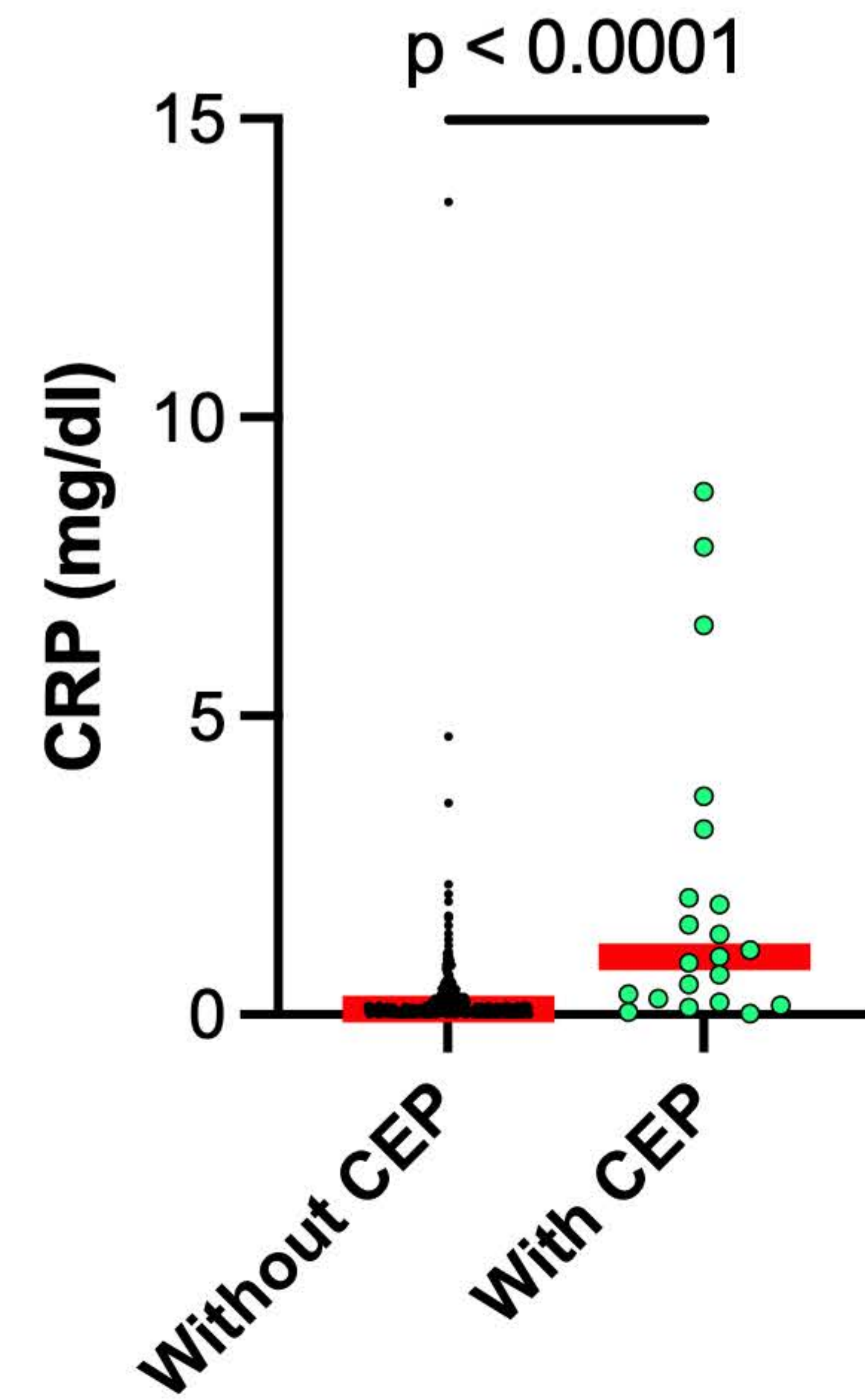
Abbreviations: BMI, body mass index; CEP, chronic eosinophilic pneumonia; CRSwNPs and CRSsNPs, chronic rhinosinusitis with and without nasal polyps; ECRS, eosinophilic chronic rhinosinusitis; ESS, endoscopic sinus surgery; HPF, high-power field; ICS, inhaled corticosteroid; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; SNOT-22, 22-item Sino-Nasal Outcome test; VAS, visual analogue scale.

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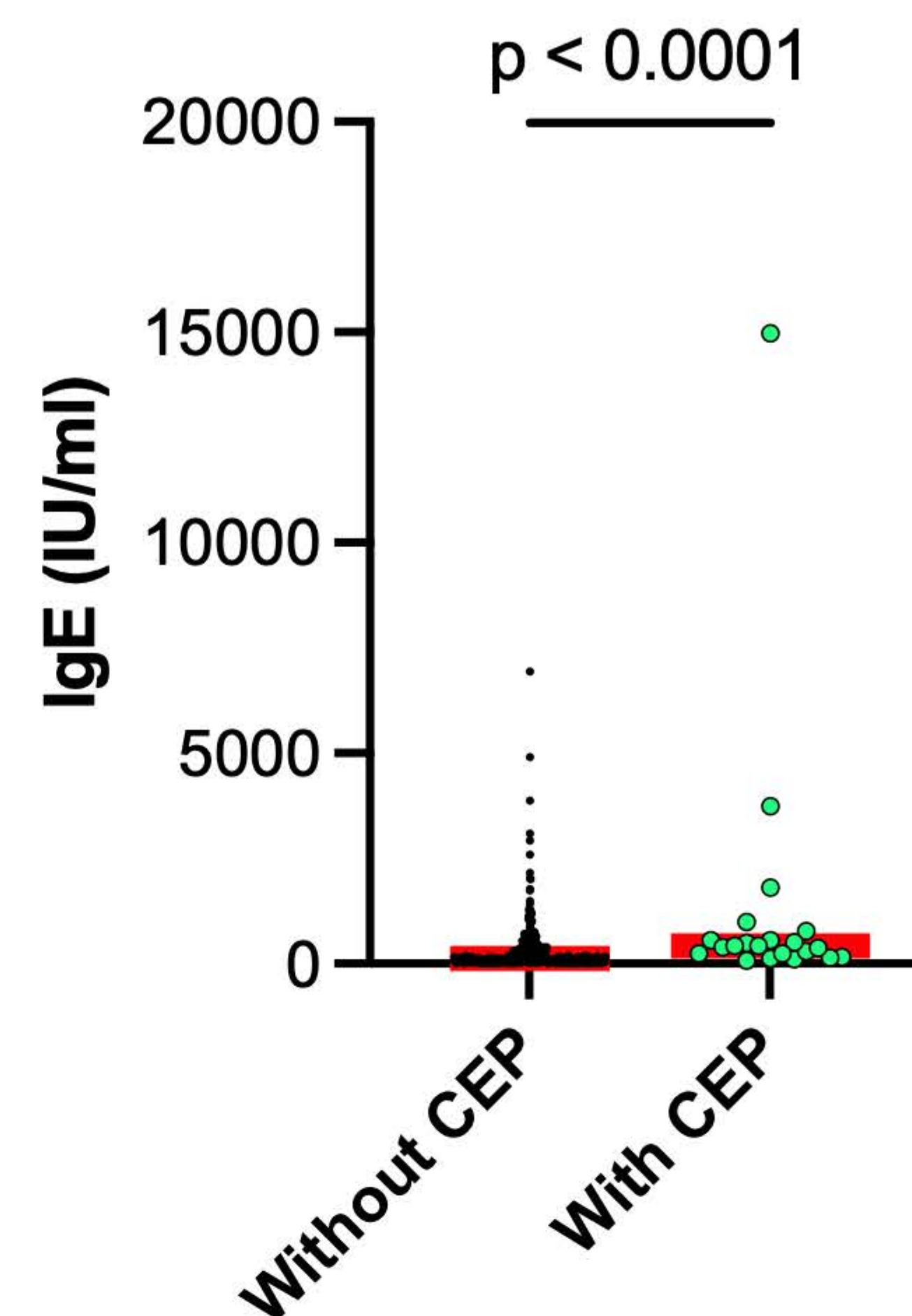
(a)



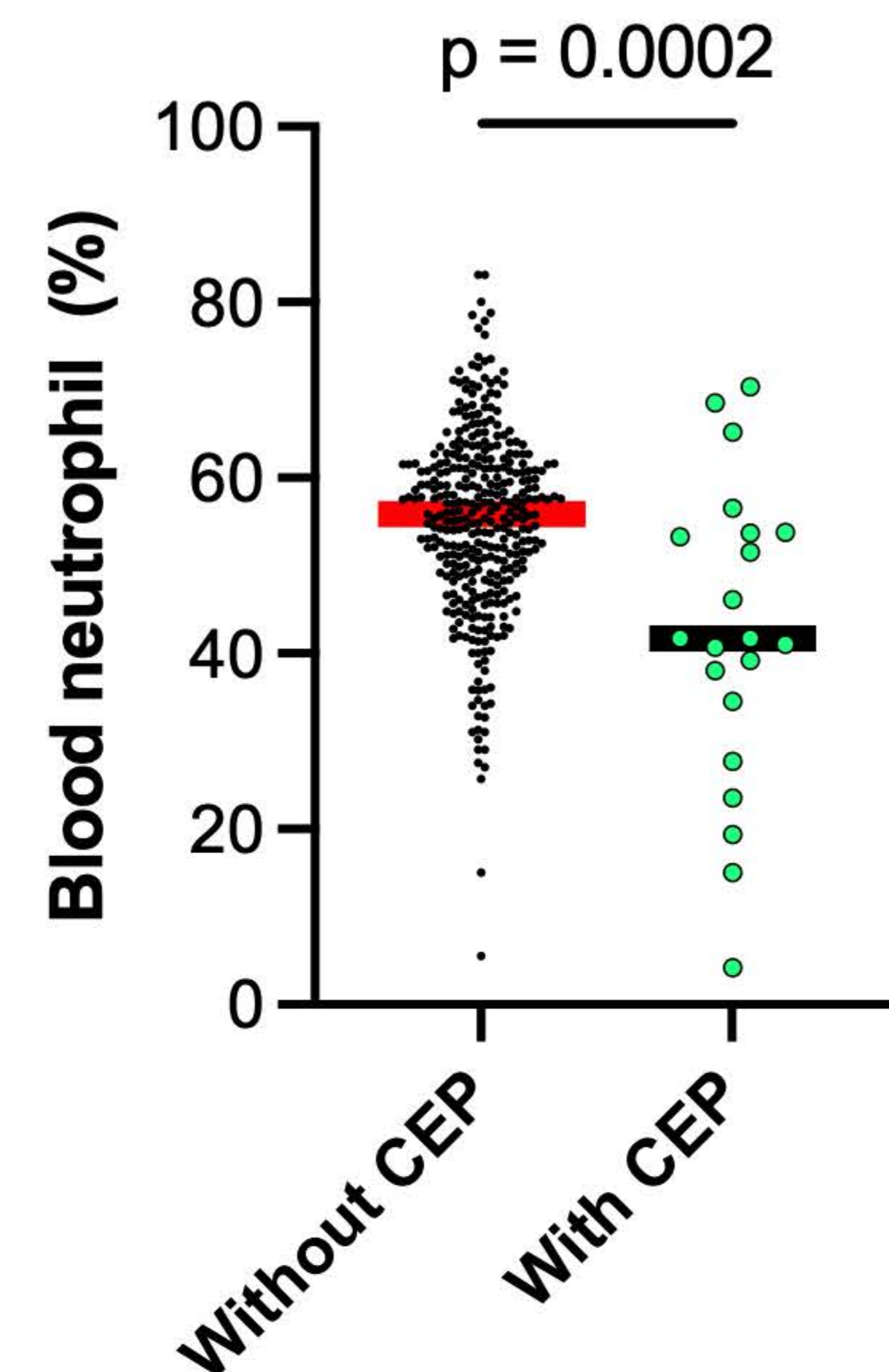
(b)



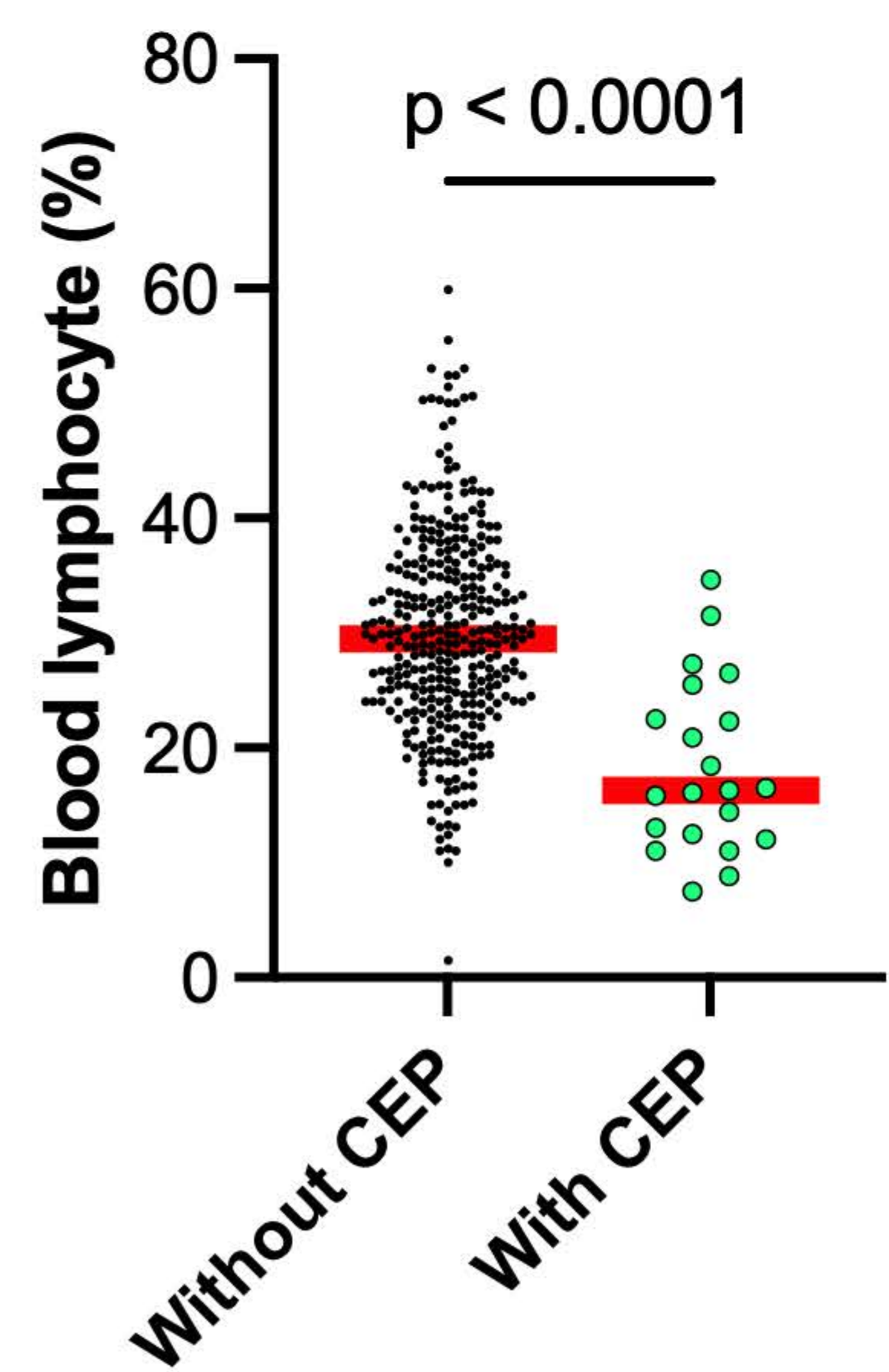
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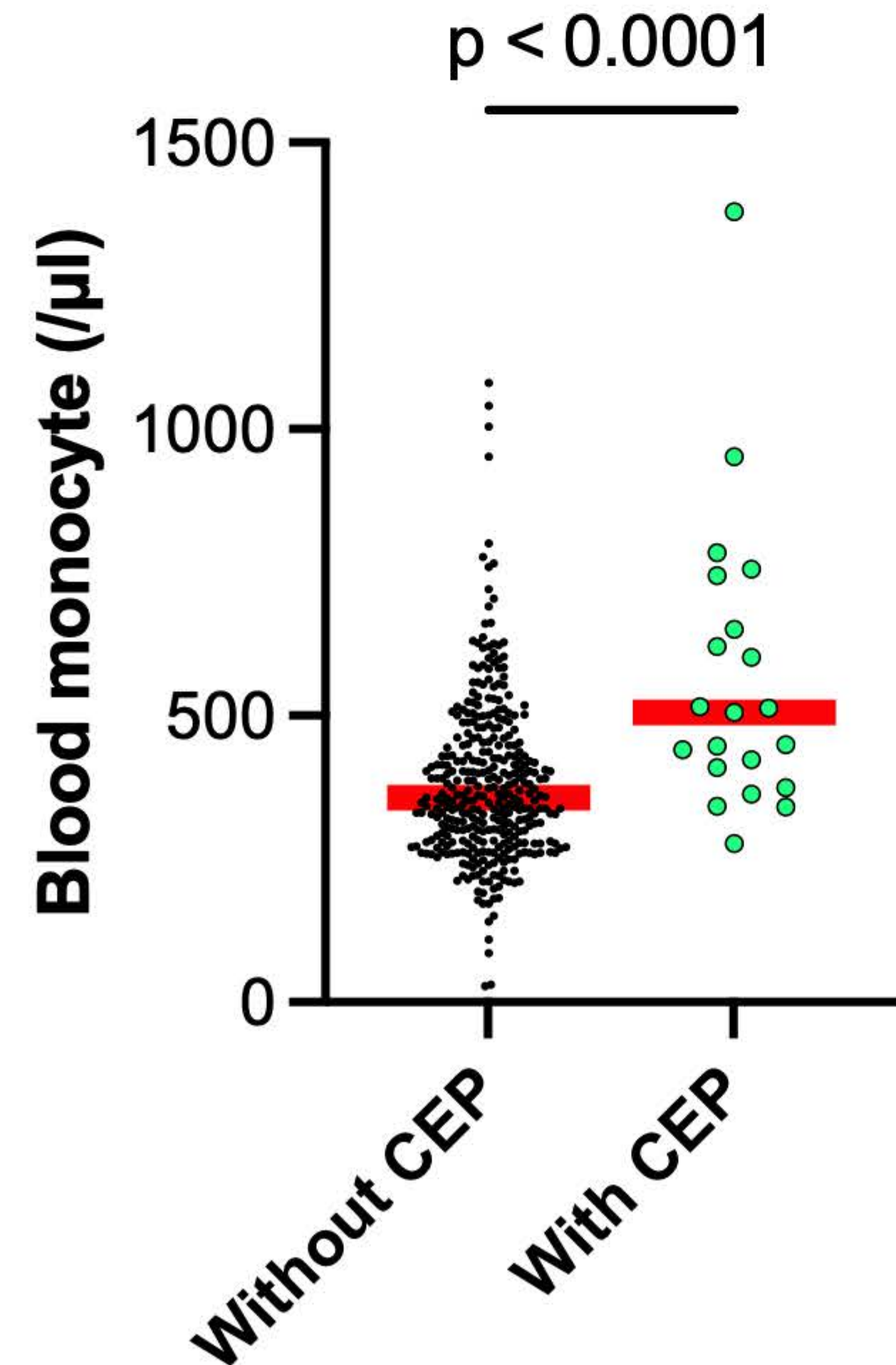
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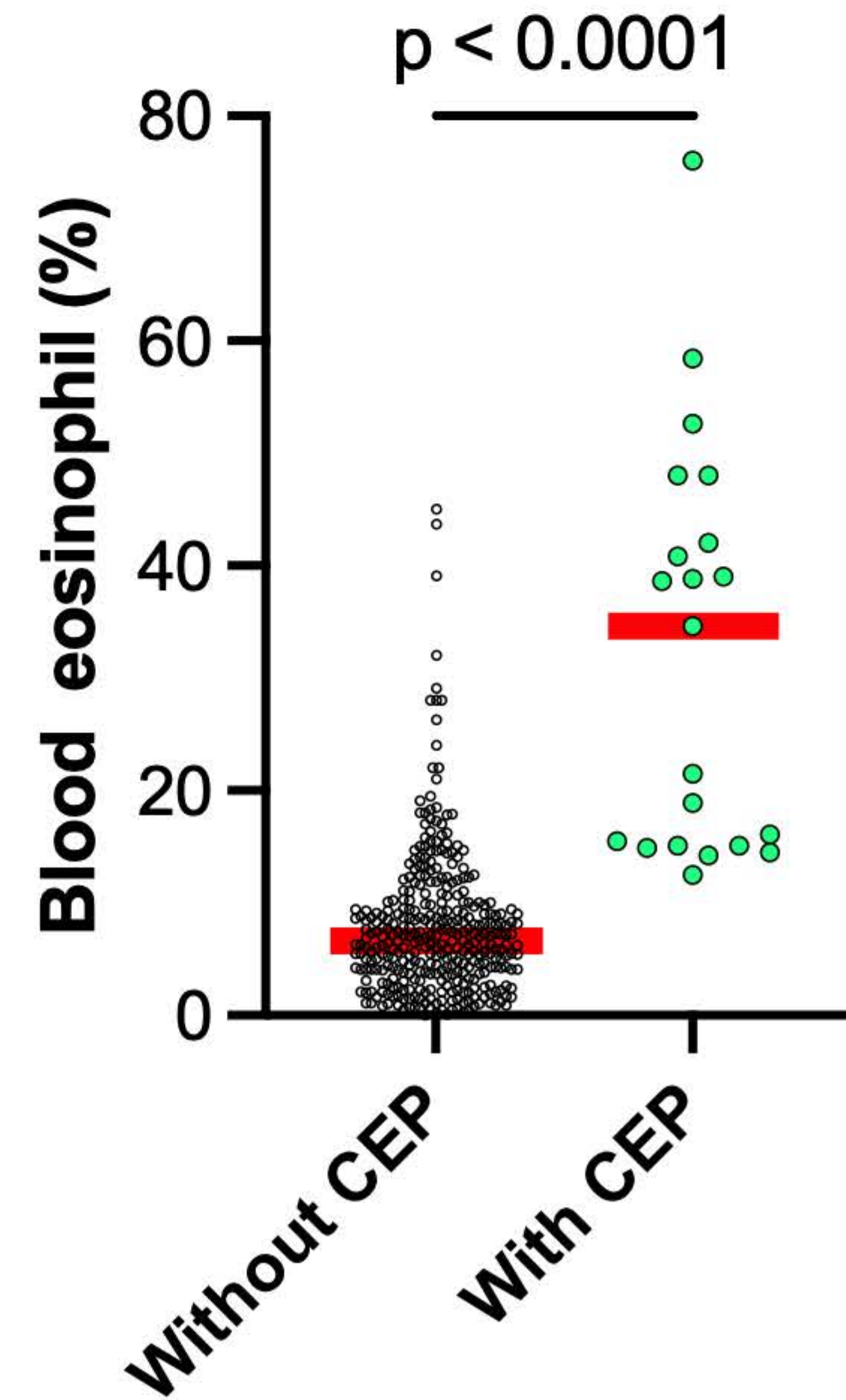
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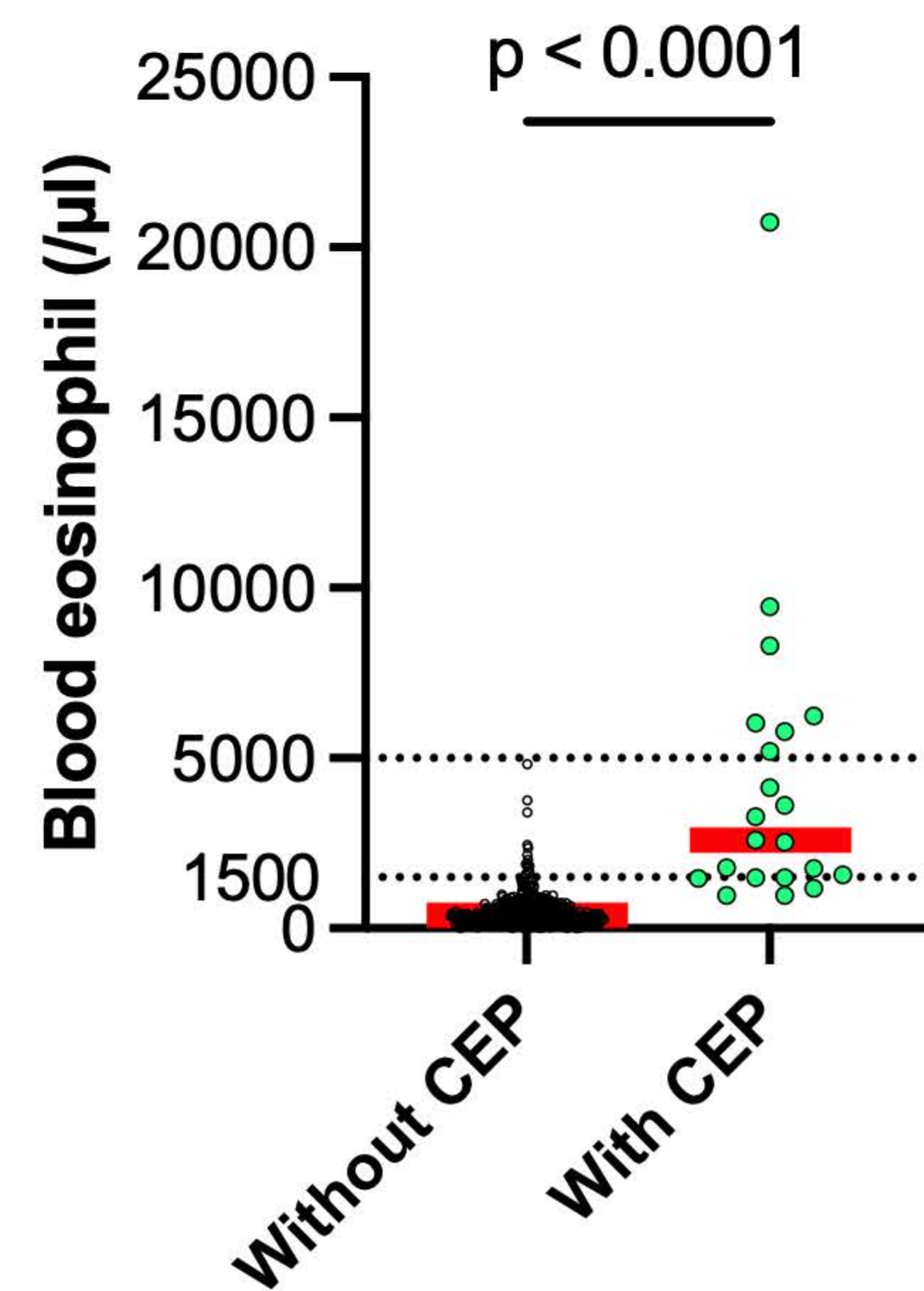
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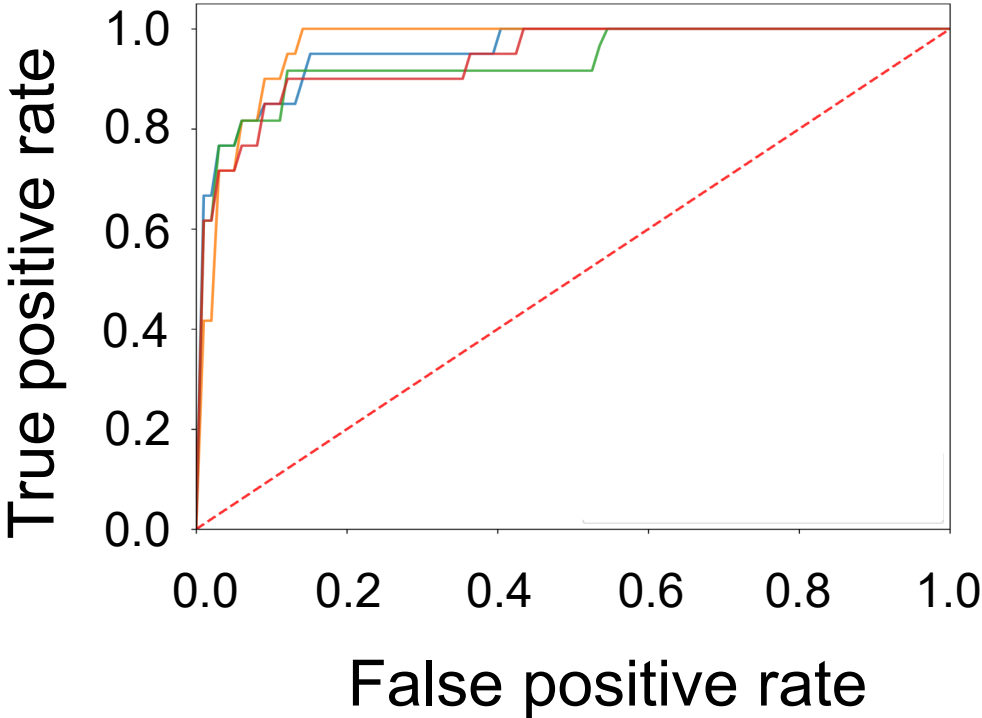
(g)



(h)

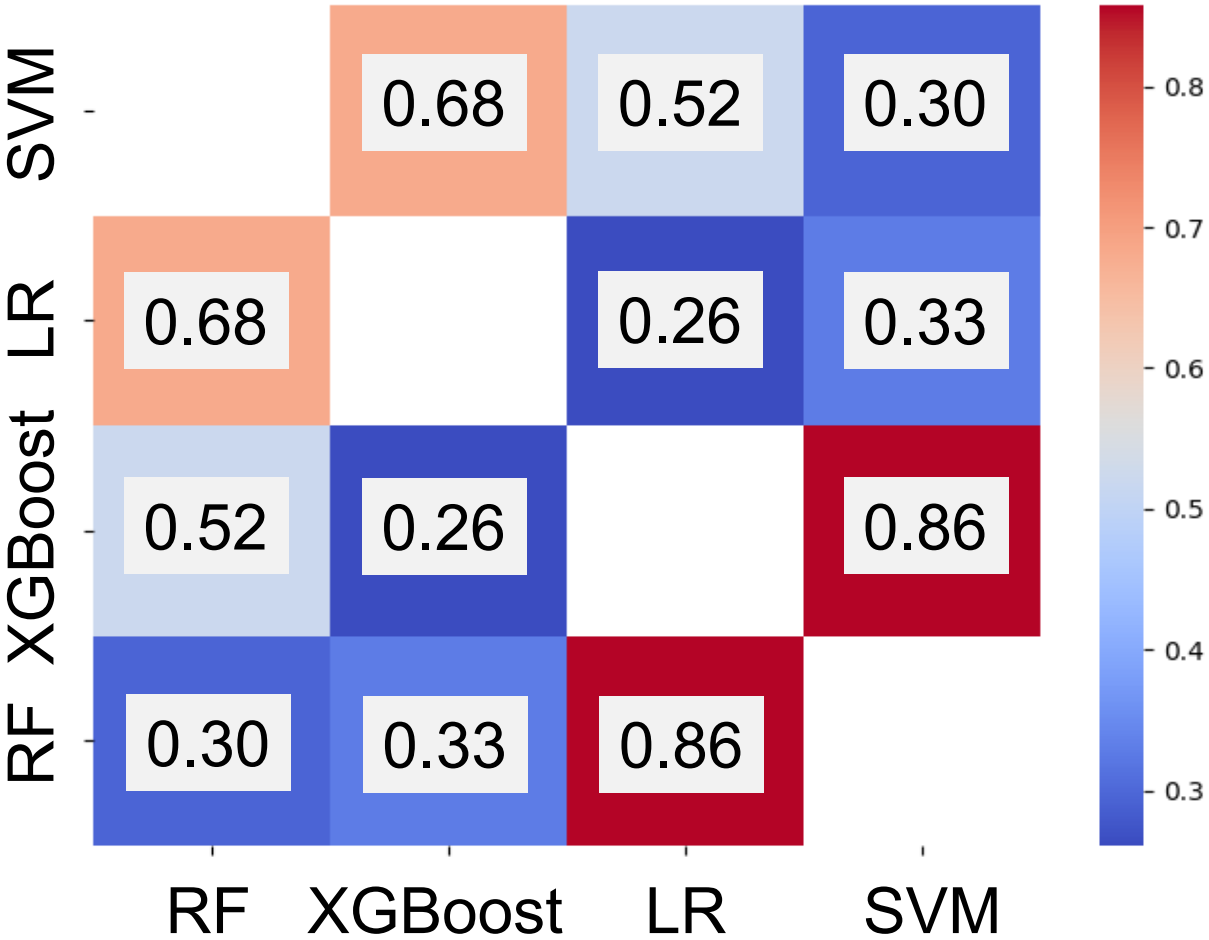


(a)



	AUC values (SD)
RF	0.957 (0.119)
XGBoost	0.966 (0.138)
LR	0.937 (0.121)
SVM	0.942 (0.126)

(b)



Eosinophil count in blood test $\leq 1446.25/\mu\text{L}$
Samples: 372
Value = (351, 21)
Class = CRS without CEP

True

False

Samples: 339
Value = (336, 3)
Class = CRS without CEP

WBC $\leq 9.25 \times 10^3/\mu\text{L}$
Samples: 33
Value = (15, 18)
Class = CRS with CEP

True

False

Samples: 11
Value = (10, 1)
Class = CRS without CEP

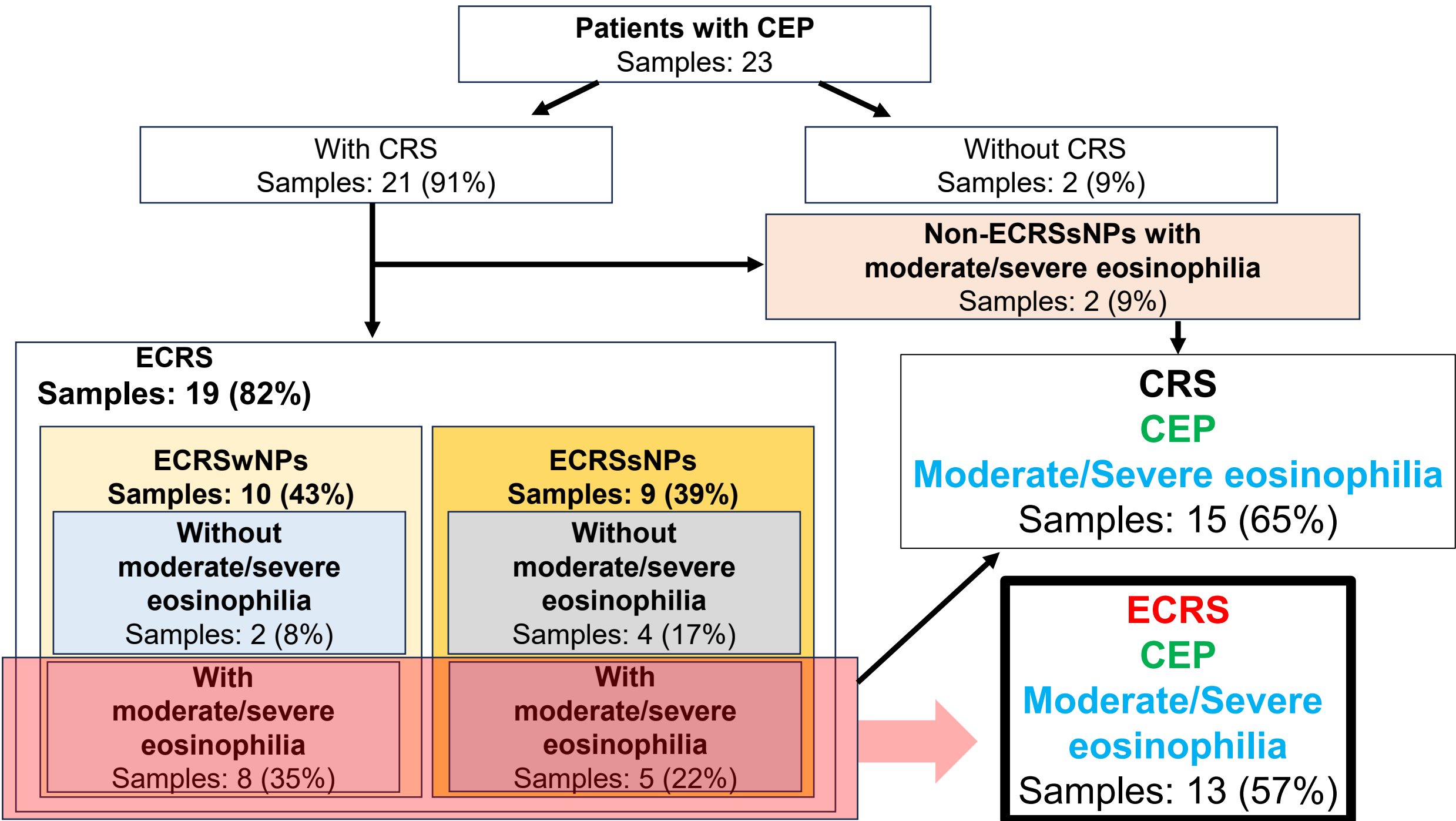
CRP $\leq 0.335 \text{ mg/dL}$
Samples: 22
Value = (5, 17)
Class = CRS with CEP

True

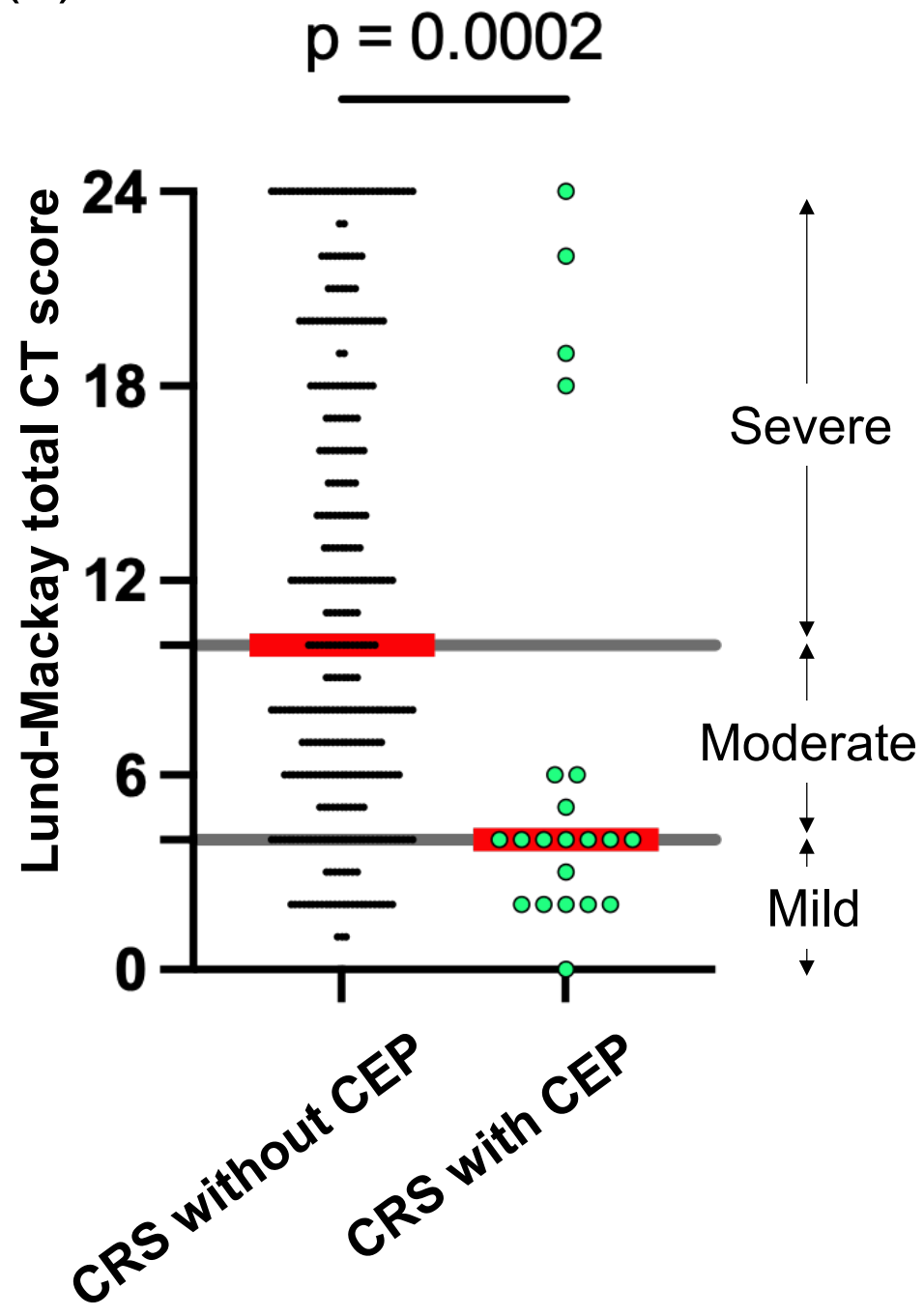
False

Samples: 10
Value = (5, 5)
Class = CRS without CEP

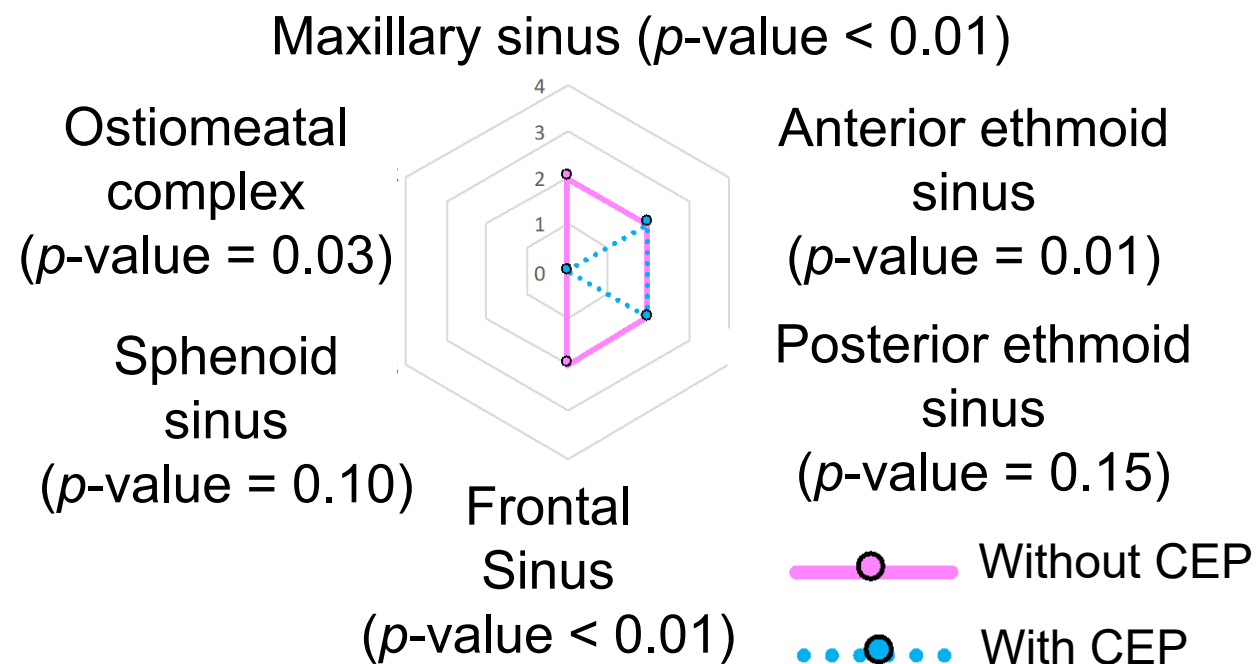
Samples: 12
Value = (0, 12)
Class = CRS with CEP



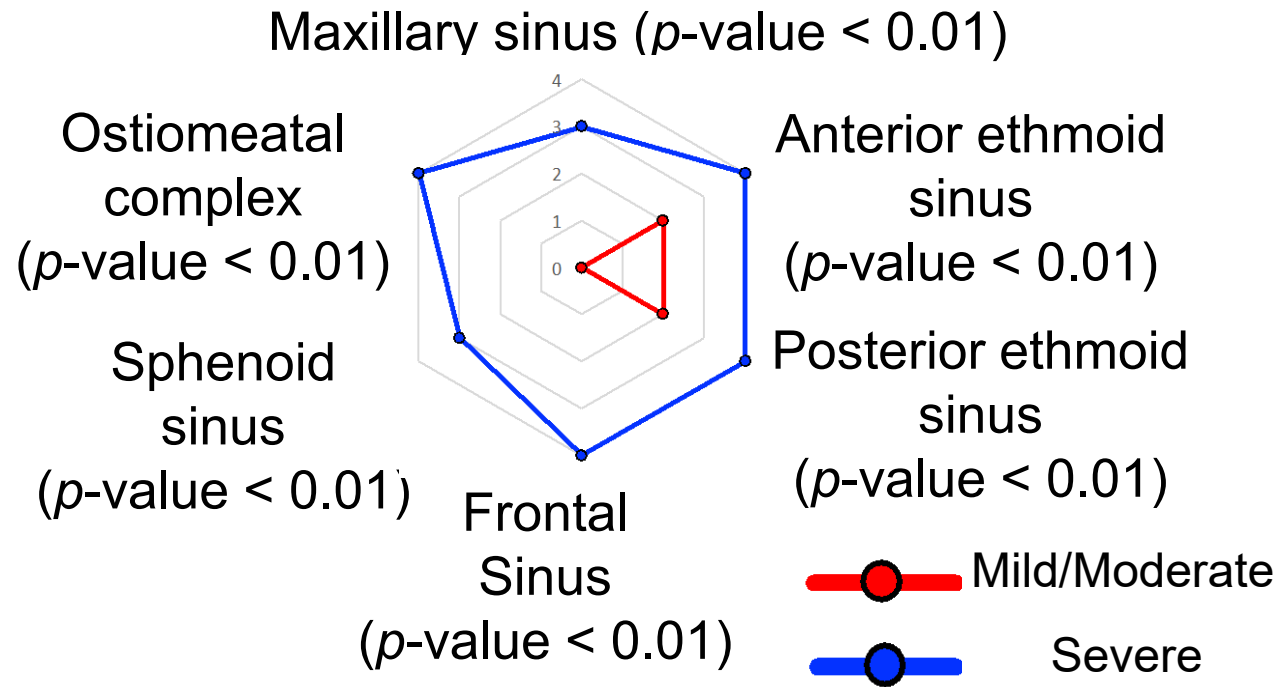
(a)



(b)

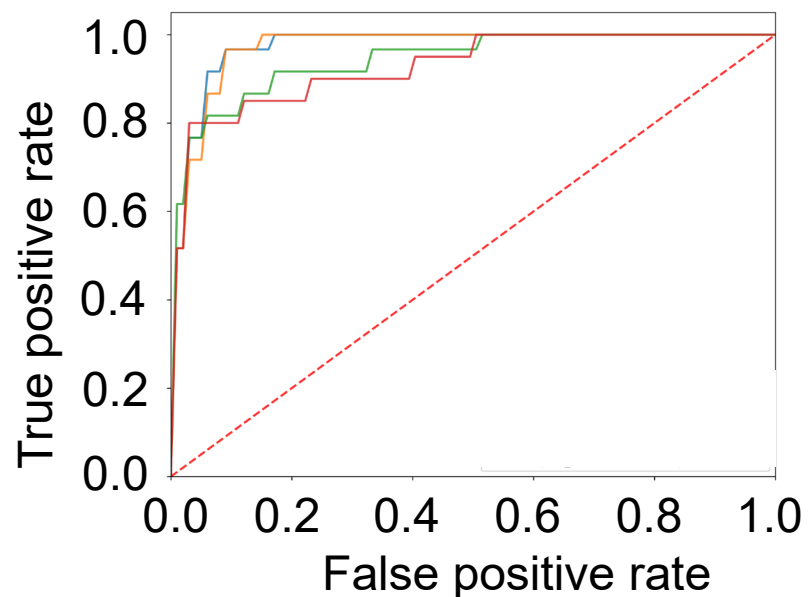


(c)



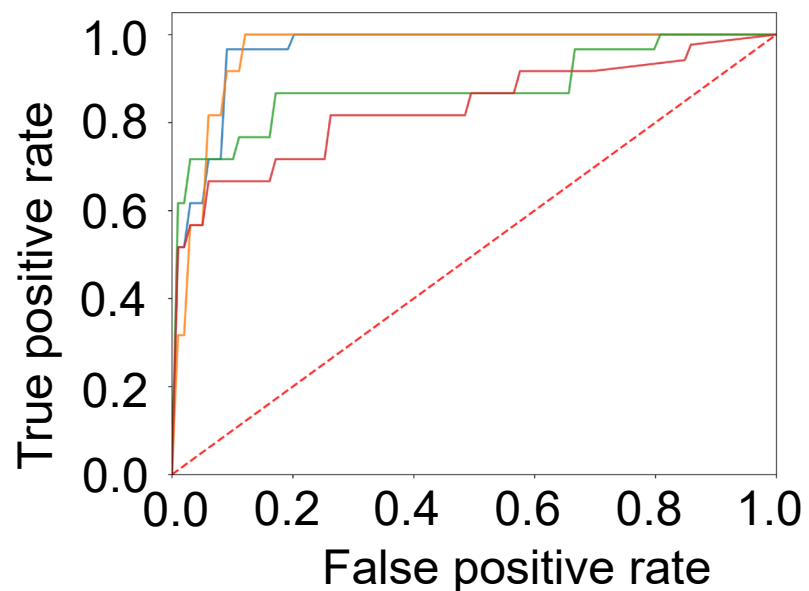
(a)

CSL



	AUC values (SD)
RF	0.974 (0.125)
XGBoost	0.973 (0.129)
LR	0.945 (0.122)
SVM	0.930 (0.130)

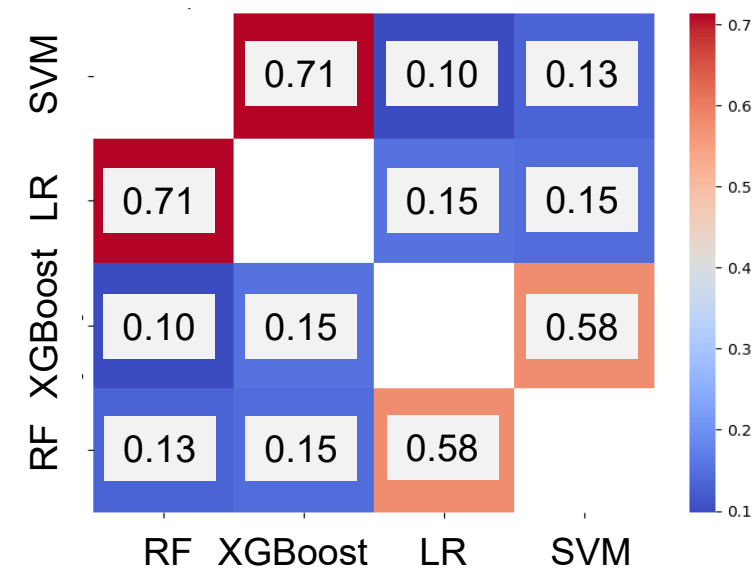
SMOTE method



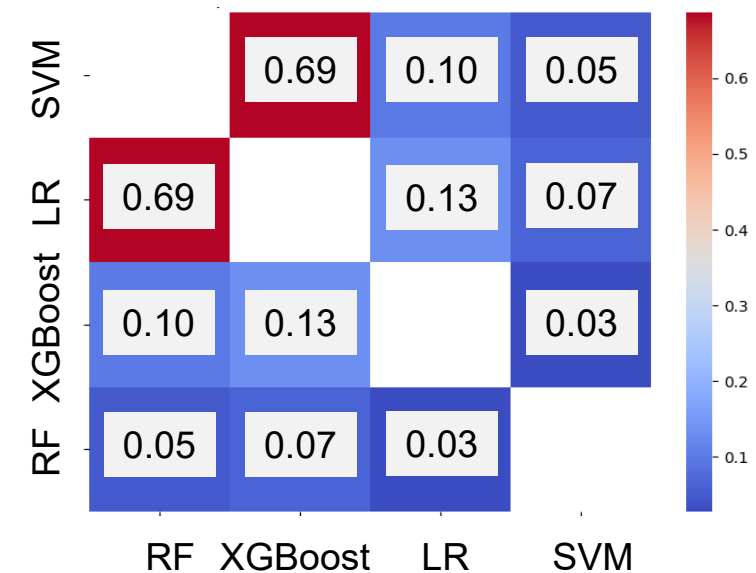
	AUC values (SD)
RF	0.960 (0.140)
XGBoost	0.961 (0.156)
LR	0.882 (0.127)
SVM	0.835 (0.146)

(b)

CSL

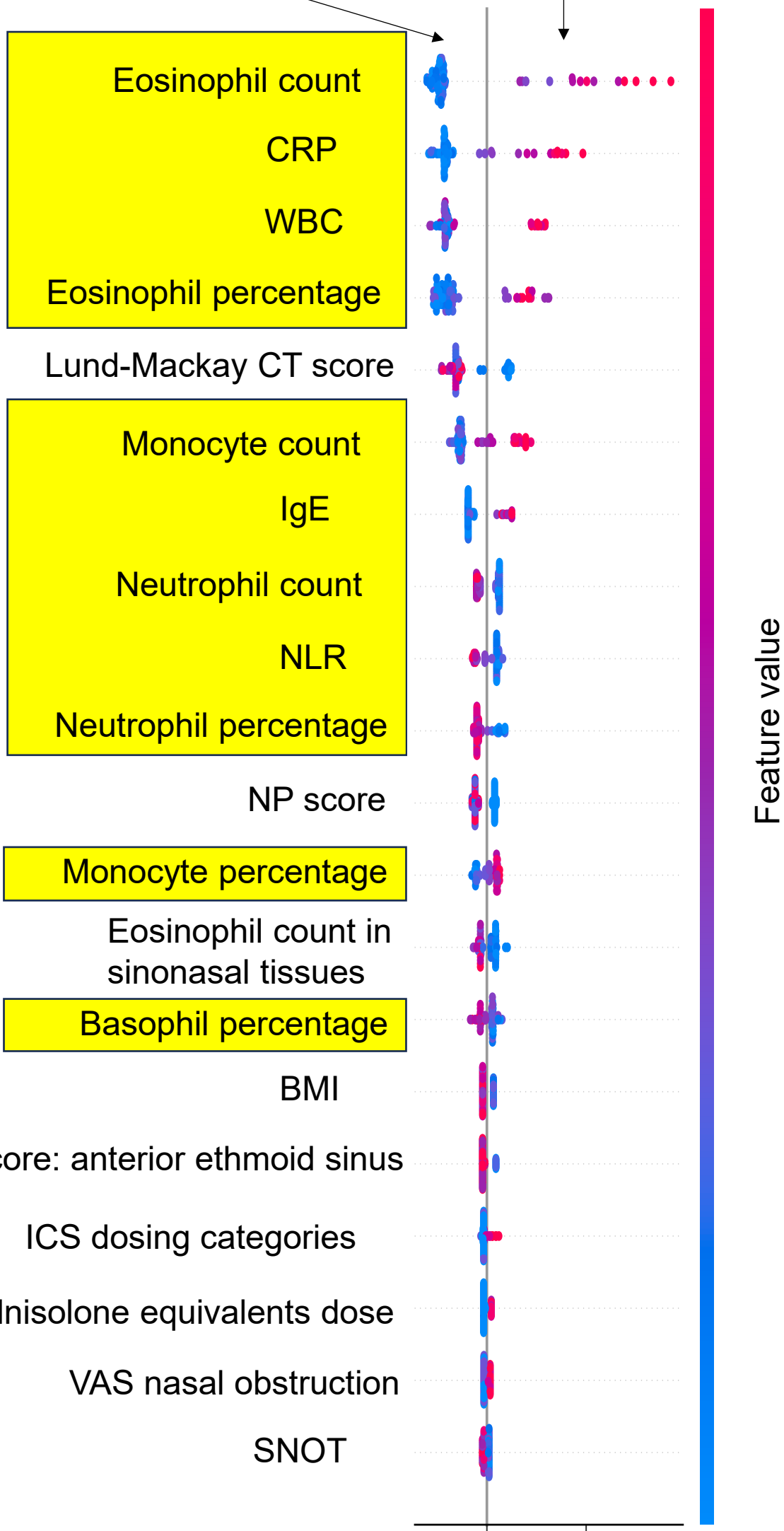


SMOTE method



Low eosinophil count (blue dots) have a negative impact on the prediction High eosinophil count (red dots) have a positive impact on the prediction

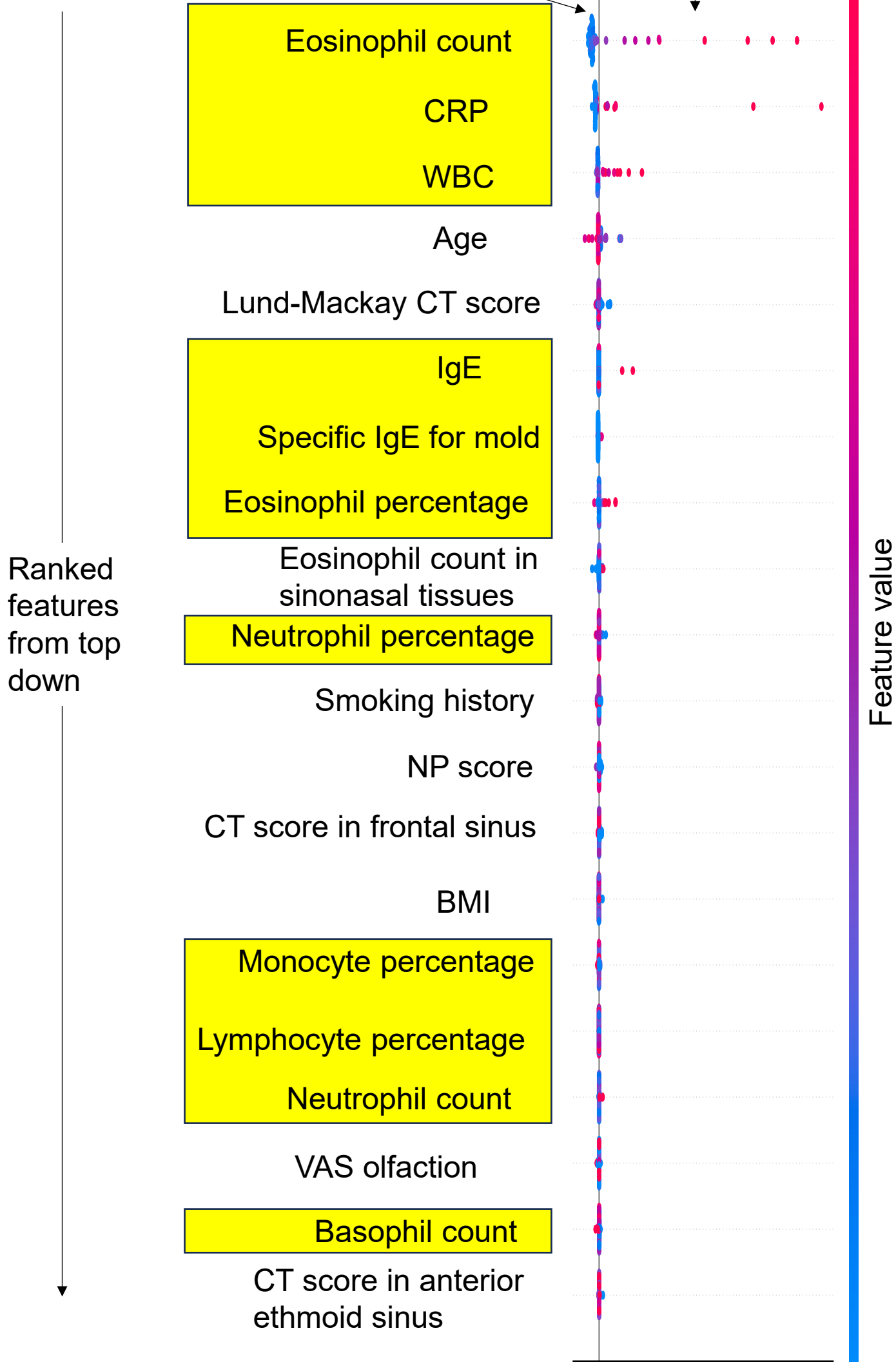
Ranked features from top down



Original XGBoost

0 2
SHAP value
(impact on model output)

Low eosinophil count (blue dots) have a negative impact on the prediction High eosinophil count (red dots) have a positive impact on the prediction



RF with CSL

0.00 0.50
SHAP value
(impact on model output)