Determining a cut-off value for eosinophilic chronic rhinosinusitis*

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Dear Editor:

Classifying eosinophilic chronic rhinosinusitis (eCRS) can be difficult. We read and commented on the article, entitled 'Achieving the best method to classify eosinophilic chronic rhinosinusitis: a systematic review' [1,2]. Toro et al. [1] precisely identified various cut-off values for tissue eosinophilia and emphasised the relevance of clinical parameters, such as recurrence with a low risk of bias. However, Pan and Liu suggested a cut-off value for eosinophilic inflammation based on the distribution of the eosinophil percentage in healthy individuals [2]. The dilemma involves defining eCRS using either reference intervals (RIs) based on healthy individuals or clinical decision limits (CDLs) based on patients. We provided suggestions from a statistical perspective. The concepts of RIs and CDLs should be distinguished. Also referred to as the 'normal range', RIs are defined as the interval between the two reference limits (2.5th and 97.5th percentiles) obtained from a healthy population with a minimum sample size of 120 (as recommended by the Clinical Laboratory Standards Institute guideline). It answers the question, 'Is the individual healthy?'. Results outside the RIs do not necessarily indicate a disease [3]. Meanwhile, CDLs are defined as values, resulting from a diagnostic test, that distinguish between two clinical subgroups [3]. In this case, the test was conducted to classify the patient between eCRS and non-eCRS. It answers the question, 'Is the patient diseased, or is the illness worsening?'[3]. RIs are based on healthy individuals, while CDLs are based on clinical outcome studies (e.g. prospective cohort studies or meta-analysis), receiver operator characteristic (ROC) curves, guidelines, and consensus values [3]. Furthermore, the ROC curve is applied when considering the sensitivity and specificity of the diagnostic test.

eCRS refers to an inflammatory phenotype, characterised by the predominance of tissue eosinophils. It is frequently associated with more severe sinus disease as well as worse surgical and medical treatment outcomes. This entity is difficult to treat because of the underlying severe eosinophilic inflammation, which is quantified using tissue eosinophils (absolute number or percentage) as biomarkers. The diagnosis of eCRS is related to CDLs. Tissue eosinophil levels above the threshold have been associated with a significantly higher risk of adverse clinical outcomes [3]. Various absolute eosinophil numbers (5–350/high power field (HPF)) and percentages (5–50%) have been used as cut-off values in the diagnostic criteria for eCRS[4]. According to Toro et al., recurrence was the most relevant parameter with a low risk of bias in the classification of eCRS. A cut-off value of 55/HPF was derived from the ROC curve with balanced sensitivity and specificity [5]. This cut-off value was further demonstrated in a meta-analysis [6]. The follow-up time for determining recurrence and postoperative medications have not been standardised. However, recurrence, detected via the routine endoscopic examination, indicates a worse response to treatment.

Tissue eosinophilia is characterised by eosinophils, larger than the upper limit of RIs. However, there is insufficient evidence, supporting that a cut-off value as low as 10% is predictive or recurrence. Setting a low threshold (8–10%) harbours the issue of increasing the population of patients diagnosed with eosinophilia and thus administered extensive treatment. Therefore, we recommend using a high outcome-related threshold to define severe eosinophilic inflammation in patients with eCRS. Using a high cut-off value of 55/HPF, the prevalence of eCRS in China and Japan was 50% and 44%, respectively [5,7]. These statistics indicated a decreased discrepancy between countries.

In summary, the cut-off values for tissue eosinophils in the diagnosis of eCRS were related to CDLs, rather than RIs. A cut-off value above the threshold was associated with a significantly higher risk of adverse clinical outcomes. Defining eCRS according to clinical parameters, such as recurrence, is important. Based on the approaches for identifying CDLs, more multicentre studies are needed to determine the optimal cut-off values at the national or international level.

Abbreviations

Clinical decision limits (CDLs); Eosinophilic chronic rhinosinusitis (eCRS); High power field (HPF); Receiver operator characteristic

(ROC); Reference intervals (RIs).

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CW and LZ were involved in the conception of the paper. LZ wrote the paper.

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