Classification of eCRS: Based on disease outcome or normal range? Comment on Toro et al.*

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Dear Editor:

Undoubtedly, there is a lack of unanimous histopathologic criteria to classify eosinophilic chronic rhinosinusitis (eCRS) worldwide. We read with great interest the recent constructive systematic review by Toro et al.[1]. The authors stretched out the current knowledge on the methods of classifying eCRS to determine an optimal cut-off point. While the authors are to be congratulated for their comprehensive overview, a point regarding the disease recurrence as the most relevant parameter to divide eosinophilic and noneosinophilic inflammation in chronic rhinosinusitis (CRS) should be discussed. In order to contribute to an evidence-based standardization of cut-off point to classify eCRS, we would like to share our considerations and approaches in this comment.

First, we agree with the authors that the use of clinical parameter like disease recurrence to classify eCRS has a significant clinical relevance. Nevertheless, the CRS recurrence is mainly determined by nasal endoscopic examination combined with symptomatic evaluation[2,3], which is influenced by the experience of physicians. The inter-physician variations in disease outcome determination will bring bias to the cut-off value generated. Second, before using disease recurrence to classify eosinophilic and noneosinophilic inflammation in CRS, a unified follow-up time period for determining CRS recurrence must be reached. Or, different cut-off values will be inevitably generated according to the different follow-up time periods. In the study by Lou et al., recurrence of nasal polyps was determined at one year after surgery, and a cut-off value of 55 eosinophils/high power filed (HPF) was genreated[2]. While Nakayama et al. followed patients for at least 6 months (the mean follow-up period was 17.5 months) and got a cut-off value of 70 eosinophils/HPF [3]. Third, CRS is a heterogenous disorder and encompasses divers endotypes. Eosinophilic inflammation is not the only cause for recurrence. Neutrophilic inflammation has also been linked with poor treatment outcome in CRS patients, particularly in Asian patients [4,5]. Therefore, to define eCRS based on recurrence has inherent limitation. Last, the CRS relapse is significantly affected by postoperative therapies. Distinct therapeutic strategies will lead to different relapse rates and thus influence the cut-off value generated. With the development and application of new treatments such as steroid-eluting sinus stents and biologics in clinic, the recurrence rate of CRS will be reduced, resulting in accompanied change of cut-off value of eCRS. With all this being stated, we think that it is difficult to establish unanimous and standard criteria for eCRS based on disease recurrence. In fact, as Toro et al outlined in their Table 1, divers cut-off values for eCRS have been reported according to disease recurrence, ranging from 55 to 80 eosinophils/HPF[1].

In contrast, we believe, to define the cut-off value for nasal eosinophilic inflammation based on the eosinophil distribution in normal subjects is a better approach. In fact, to develop normal range and thus to derive cut-off value are a widely and commonly used approach for defining a disease status[6]. The normal range and the cut-off value for a disease status are generated based on normal subjects, but not patients; therefore, these values are more likely to be consistently generated by different studies, which would not be biased by disease relevant factors, such as treatments. To use the percentage of eosinophils in total inflammatory cells instead of absolute counts of eosinophils in nasal tissues reduces the potential bias introduced by the mixed inflammation as concerned by Toro et al. In the reports of Cao and Jiang et al., the cut-off value was calculated as twice the standard deviation of the mean of eosinophil percentage in control subjects, and 10% and 8% value were generated, respectively[7,8]. The cut-off value of 10% proposed by Cao et al. has been widely used in the published researches as shown by Figure 3 in Toro's paper[1]. Based on this cut-off, it has been demonstrated that eosinophilic and noneosinophilic nasal polyps have distinct clinical features, prognosis, and immune profiles of T cells, dendritic cells, and isotypes of local immunoglobulins[9]. In the review by Toro et al., the authors used Quality Assessment Tool to assess methodological quality of 13 original cut-off studies, and concluded that studies using twice the standard deviation of the mean controls had a great risk of bias[1]. However, we want

to emphasize that the Quality Assessment Tool is a tool to assess quality of study design, and it is unable to judge the rationality of the approaches to develop cut-off values. In addition, some items in Quality Assessment Tool are incomparable between the studies with different cut-off defining approaches. For example, regarding the Q13 (was loss to follow-up after baseline 20% or less?), there was no need of follow-up in the studies by Cao and Gao et al.[7,8].

In summary, different approaches to classify eCRS should be thoroughly discussed, and international collaborations are helpful to elaborate this issue.

Abbreviations

CRS, chronic rhinosinusitis; eCRS, eosinophilic chronic rhinosinusitis.

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All authors meet the criteria for the authorship. ZL conceived and edited the manuscript, LP wrote the manuscript.

Conflict of interest

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