Reply to Letter to the editor concerning "Achieving the best method to classify Eosinophilic Chronic Rhinosinusitis: a systematic review"*

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Dear Editor:

When drafting the article "Achieving the best method to classify eosinophilic chronic rhinosinusitis "[(1)], our main goal was to draw attention to the heterogeneity of methods and classifications of Eosinophilic Chronic Rhinosinusitis (eCRS) over the centers around the globe [(1)]. We thank Li Pan and Zheng Liu's letter to the editor for further enriching the discussion on this topic and for the valuable comments [(2)].

There was a variety of methods described in the literature concerning the number of high-powered fields, observers and drugs restriction prior to biopsy for classifying eCRS. However, deciding the best reference to establish a cut-off point for tissue eosinophils was the main challenge. The use of eosinophil distribution in normal subjects, as a reference parameter, is well documented in the literature for blood eosinophils and bronchial lavage, but not for tissue histology[(3,4)].

In our systematic review, two studies used the eosinophil tissue count distribution in normal subjects to establish a cut-off point, and even considering that both evaluated Chinese individuals, there was still a variation of 8% and 10 % in the cut-off point[(5,6)]. It is also memorable that both studies had a low number of controls (50 in the Cao study and 10 in the Jiang study)[(5,6)], which can induce low statistical relevance. Furthermore, there is no way to affirm that it would be the same cut-off point for other populations, specially assuming that Asiatic descendants may depict polyps with the mixed Type 1 and Type 3 patterns more than Causasians[(7)].

Although the standard deviation may differentiate an endotype dominance in type 2 inflammation, it does not necessarily correlate to the eCRS phenotype associated with a poorer prognosis and recurrence [(8-10)]. A higher number of eosinophil count in the range of 50-80 eos / HPF was not only found when considering recurrence alone but also in the cluster analysis that used different parameters as asthma, allergy, inflammatory phenotypes, and CT scores [(9, 11-15)].

It is known that eosinophilic inflammation can be driven by both allergic-dependent and allergic-independent paths, and non-atopic eosinophilic chronic rhinosinusitis may be a difficult to treat phenotype [(16,17)]. Xiang et al. demonstrated that CRS patients with comorbid allergic rhinitis had increased eosinophil tissue count comparing with those without allergic rhinitis, and Gao et al. also demonstrated a higher eosinophil count in atopic patients [(18,19)]. So, we can conclude that when evaluating eosinophilic infiltration alone, without considering clinical features, we may find a lower cut-off point for eCRS, which can be possibly associated with an atopic profile rather than a recurrent or difficult to treat phenotype.

The use of the Quality assessment tool for observational cohort and cross-sectional studies is a validated tool that can be used to evaluate risk of bias in the selected articles [(20)]. The use of this methodological quality assessment tool aimed to verify the risk of bias in the studies in different aspects, thus verifying whether the items were clearly met. We considered this tool as the most appropriate for the 13 studies, due to the heterogeneity of the articles. This instrument was not intended to assess the cut-off point used in the studies, but rather the risk of bias regarding its methodological structure, with structured and well-defined questions. Q13 of the tool regarded follow-up of the patients. In this item of the instrument, Cao et al. [(6)] and Gao et al. [(19)] studies were stated as "not applicable" since no follow up was needed, according to the study design. However, in researches that used recurrence to define a cut-off point, loss of follow-up was an important resource of bias.

We agree with Li Pan and Zheng Liu that there is a lack of standardization regarding time of follow-up and classification of recurrence, favoring bias. For this reason, an international collaboration is needed to best approach a cut-off point and systematize clinical and histological methods for this classification.

Abbreviations

eCRS: eosinophilic chronic rhinosinusitis

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