

Original Article

Relationship between histologic changes and inflammatory markers in chronic rhinosinusitis

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Abstract: The present study aimed to elucidate the relationship between histologic changes and inflammatory markers in chronic rhinosinusitis (CRS). Inflammatory markers of CRS, including eosinophil and neutrophil counts, the eosinophil-to-lymphocyte ratio, and the neutrophil-to-lymphocyte ratio, were investigated in tissues and peripheral blood. Inflammatory markers were evaluated according to the histologic changes of stromal edema, stromal fibrosis, and basement membrane (BM) thickening. Among 92 patients with CRS who underwent pathologic examinations, stromal edema, stromal fibrosis, and BM thickening were identified in 84.8%, 25.0%, and 53.3% of patients, respectively. Stromal edema and BM thickening were observed more frequently in CRS with nasal polyps than in CRS without nasal polyps ($P = 0.001$ and $P = 0.001$, respectively). Tissue inflammatory markers differed according to the presence of histologic changes in tissues. In peripheral blood, however, only the eosinophil count differed according to BM thickening. Patients with two or more histologic changes had higher tissue eosinophil-to-lymphocyte ratios ($P = 0.008$) and eosinophil counts ($P = 0.002$) compared with subjects with no or one histologic change. Conversely, the tissue neutrophil-to-lymphocyte ratio and neutrophil count were higher in patients with no or one histologic change than in patients with two or more changes. Collectively, tissue inflammatory markers may be correlated with histologic changes in CRS. However, serum inflammatory markers have a limited ability to predict histologic changes in patients with CRS.

Keywords: Chronic rhinosinusitis, nasal mucosa, inflammatory marker, eosinophils, histologic change, tissue remodeling

Introduction

Chronic rhinosinusitis (CRS) is defined as symptomatic inflammation of sinonasal mucosa persisting for more than 12 weeks [1]. CRS is a common disease associated with considerably impaired quality of life, reduced work productivity, and increased medical treatment cost [2]. In general, CRS is classified as CRS with nasal polyps (CRS_{WNPs}) and without nasal polyps (CRS_{sNPs}). Although the cause of CRS remains unclear, mucosal inflammation and its consequences have been reported as factors distinguishing the different clinical phenotypes [3]. Characterizing CRS pathology based on infiltrating inflammatory cell profiles such as eosinophils or neutrophils, differentiated T cell patterns, and tissue remodeling patterns might help identify distinct disease entities of CRS [2].

Based on the underlying inflammatory process, CRS can also be classified as eosinophilic and non-eosinophilic [4]. Tissue eosinophilia is a representative predictor of a poor prognosis associated with a high recurrence of nasal polyps and persistent postoperative symptoms [5]. However, the cutoff eosinophil count for defining eosinophilic CRS varies among studies, ranging from 5 to 120 eosinophils per high power field [6, 7]. In addition, within tissues, eosinophil counts can vary based on differences in the counting foci determined by investigators.

In previous studies, the roles of inflammation and tissue remodeling in the pathogenesis of airway diseases such as asthma and CRS have been reported [3]. The structural changes caused by tissue remodeling in CRS include squamous metaplasia, basement membrane

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(BM) thickening, stromal edema and fibrosis, and goblet cell hyperplasia, as well as subepithelial gland hyperplasia [8]. In previous studies, the relationship between inflammation and tissue remodeling was reportedly not a simple cause-effect relationship but a complex association involving multiple pathways [9]. However, the relationship between these histologic changes and inflammatory markers in CRS remains unclear.

In the present study, the inflammatory markers associated with histologic changes in CRS were investigated. In addition, a subgroup analysis according to the CRS phenotype was performed.

Materials and methods

Patients

The medical records of 92 patients who underwent endoscopic sinus surgery and concurrent biopsy for CRS between March 1, 2017 and July 31, 2019 were analyzed. Glass slides of biopsied tissues were reviewed for histologic changes and infiltrating inflammatory cell counts. In addition, medical charts were reviewed to collect patient clinical information, including demographics, comorbid conditions, and results of laboratory tests. A blood sample to measure eosinophil, lymphocyte, and neutrophil counts and percentages was obtained from all patients. This protocol was reviewed and approved by the Institutional Review Board of Eulji University Hospital (Approval No. EMC 2019-08-001).

Histologic changes

Histologic review of hematoxylin- and eosin-stained slides was performed by a pathologist (J.S.P), who was blinded to the clinical history. Histologic changes in terms of stromal edema, stromal fibrosis, and BM thickening were investigated. Each histologic change was evaluated as present or absent, regardless of severity or extent. Based on the severity of the histologic changes, the tissue remodeling group was defined as showing two or more histologic changes. In addition, squamous metaplasia of the pseudostratified ciliated columnar epithelium was evaluated.

Inflammatory markers

As inflammatory markers, eosinophil and neutrophil counts, the eosinophil-to-lymphocyte ratio (ELR), and the neutrophil-to-lymphocyte ratio (NLR) were measured in tissues and peripheral blood. Tissue inflammatory marker levels are expressed as the mean values of three hotspots. Inflammatory markers in peripheral blood were examined preoperatively.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The differences between groups in terms of nominal variables such as the presence of nasal polyps, presence of inflammatory markers, sex, and histologic changes were determined using the two-sided χ^2 test. The differences between groups in terms of histologic changes and numerical variables including age and inflammatory markers was performed using the two-tailed Student's *t*-test. A *P*-value < 0.05 was considered statistically significant.

Results

Patient characteristics associated with histologic changes

Figure 1 shows representative images of histologic changes and inflammatory cell infiltrates in CRS tissues. Among the 92 patients with CRS, 78 (84.8%), 23 (25.0%), and 49 (53.3%) exhibited stromal edema, stromal fibrosis, and BM thickening, respectively. No differences in the presence of histologic changes according to age or sex were observed (**Table 1**). The patients with CRSwNPs showed significantly higher rates of stromal edema and BM thickening compared with those with CRSsNPs (*P* = 0.001 and *P* = 0.001, respectively). However, no difference in stromal fibrosis between the CRSwNP and CRSsNP groups was observed.

Inflammatory markers based on histologic changes

In tissues, the infiltrating eosinophil count and ELR in tissues differed according to the histologic changes (**Table 2**), with significant increases observed in tissues with stromal edema and BM thickening but decreases in tissues with

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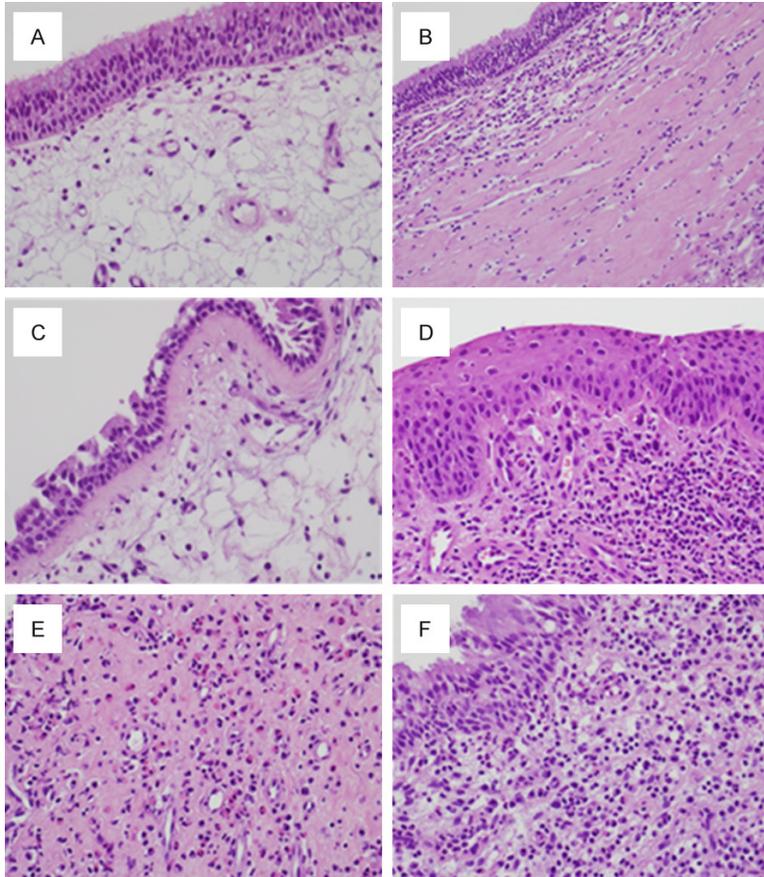


Figure 1. Representative images showing histologic changes and inflammatory cell infiltration in chronic rhinosinusitis: (A) stromal edema, (B) stromal fibrosis, (C) basement membrane thickening, (D) squamous metaplasia, (E) eosinophil infiltration, and (F) neutrophil infiltration ($\times 400$).

stromal fibrosis. The infiltrating neutrophil count and NLR were significantly decreased in tissues with stromal fibrosis and BM thickening but not in those with stromal edema. Among the serum inflammatory markers, only the eosinophil count was significantly increased in the presence of BM thickening. However, other serum inflammatory markers, such as the neutrophil count, NLR, and ELR, were not affected by the histologic changes. Furthermore, there were no differences in the levels of inflammatory markers according to the presence of squamous metaplasia (data not shown).

Subgroup analyses according to the presence of nasal polyps were also performed. In CRSwNPs, the eosinophil count and ELR were significantly increased in tissues exhibiting BM thickening, whereas the ELR was significantly decreased in tissues exhibiting stromal fibrosis (Table 3). In CRSsNPs, the neutrophil count and

NLR were significantly decreased in tissues with stromal fibrosis and BM thickening, whereas the NLR was increased in tissues with stromal edema (Table 4). On the other hand, these inflammatory markers in serum were not associated with any histologic change in either CRSwNPs or CRSsNPs.

Patients with two or more histologic changes showed significantly higher tissue eosinophil counts ($P = 0.002$) and ELRs ($P = 0.008$) (Figure 2A and 2B) but lower tissue neutrophil counts ($P = 0.001$) and NLRs ($P = 0.037$) (Figure 2C and 2D) compared with patients with no or one histologic change.

Discussion

In this study, the relationship between histologic changes and various inflammatory markers in the tissues and peripheral blood of patients with CRS was analyzed. Our findings can be summarized as follows. First, stromal edema and BM thickening were observed more frequently in CRSwNPs than in CRSsNPs. Second, irrespective of the CRS subtype, stromal edema and BM thickening were accompanied by tissue eosinophilia and a high tissue ELR, whereas stromal fibrosis was accompanied by decreased inflammatory marker levels. Third, the histologic changes were associated with eosinophil-related markers in CRSwNPs and with neutrophil-related markers in CRSsNPs. In the presence of BM thickening, the tissue eosinophil count and ELR were increased in CRSwNPs, whereas the tissue neutrophil count and NLR were decreased in CRSsNPs. Fourth, CRS with two or more histologic changes was associated with a higher tissue eosinophil count and ELR but a lower tissue neutrophil count and NLR compared with CRS with no or one histologic change. Finally, the histologic changes differed significantly according to the tissue but not serum inflammatory markers.

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Table 1. Patient characteristics according to histologic changes

	Stromal edema		P-value	Stromal fibrosis		P-value	BM thickening		P-value
	Present	Absent		Present	Absent		Present	Absent	
Total (n = 92)	78 (84.8)	14 (15.2)		23 (25.0)	69 (75.0)		49 (53.3)	43 (46.7)	
Age, years	45.7±14.2	50.6±20.1	0.268	42.6±13.8	47.8±15.5	0.160	48.2±14.4	44.5±16.0	0.247
Sex									
Male	59 (88.1)	8 (11.9)	0.152	20 (29.9)	47 (70.1)	0.079	38 (56.7)	29 (43.3)	0.277
Female	19 (76.0)	6 (24.0)		3 (12.0)	22 (88.0)		11 (44.0)	14 (56.0)	
Diagnosis									
CRSwNP	62 (92.5)	5 (7.5)	0.001	16 (23.9)	51 (76.1)	0.685	43 (64.2)	24 (35.8)	0.001
CRSSNP	16 (64.0)	9 (36.0)		7 (28.0)	18 (72.0)		6 (24.0)	19 (76.0)	

Numbers in parentheses represent percentages. Bold P-values represent significant differences. BM, basement membrane; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSSNP, chronic rhinosinusitis without nasal polyps.

Table 2. Inflammatory marker levels according to histologic changes in chronic rhinosinusitis

	Stromal edema		P-value	Stromal fibrosis		P-value	BM thickening		P-value
	Present	Absent		Present	Absent		Present	Absent	
Eosinophil count	40.47±55.36	10.12±14.50	< 0.001	19.20±29.85	41.41±57.08	0.019	52.32±63.92	17.09±24.46	0.001
ELR	2.02±3.52	0.18±0.28	< 0.001	0.61±1.00	2.12±3.71	0.003	2.63±4.14	0.73±1.48	0.004
Neutrophil count	17.40±23.59	14.74±24.99	0.701	8.09±11.31	19.97±25.96	0.003	8.99±12.25	26.12±29.73	0.001
NLR	0.87±2.07	0.23±0.32	0.251	0.21±0.31	0.96±2.18	0.007	0.37±0.70	1.24±2.65	0.041

Numerical data are expressed as means ± standard deviation. Bold P-values represent significant differences. BM, basement membrane; ELR, eosinophil-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 3. Inflammatory marker levels according to histologic changes in chronic rhinosinusitis with nasal polyps

	Stromal edema		P-value	Stromal fibrosis		P-value	BM thickening		P-value
	Present	Absent		Present	Absent		Present	Absent	
Eosinophil count	46.41±59.64	13.67±20.17	0.229	25.67±33.95	49.71±63.12	0.151	58.61±65.77	17.74±26.48	0.001
ELR	2.38±3.84	0.27±0.44	0.226	0.83±1.13	2.66±4.15	0.006	2.97±4.32	0.90±1.80	0.008
Neutrophil count	13.48±20.25	8.20±9.81	0.568	6.90±9.37	15.03±21.63	0.150	9.72±12.76	19.11±27.44	0.124
NLR	0.82±2.23	0.17±0.21	0.519	0.20±0.29	0.95±2.44	0.228	0.40±0.74	1.43±3.40	0.158

Numerical data are expressed as means ± standard deviation. Bold P-values represent significant differences. BM, basement membrane; ELR, eosinophil-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 4. Inflammatory marker levels according to histologic changes in chronic rhinosinusitis without nasal polyps

	Stromal edema		P-value	Stromal fibrosis		P-value	BM thickening		P-value
	Present	Absent		Present	Absent		Present	Absent	
Eosinophil count	17.48±23.66	8.15±11.22	0.280	4.43±4.43	17.89±22.85	0.027	7.28±10.49	16.28±22.35	0.355
ELR	0.62±1.00	0.13±0.16	0.158	0.11±0.13	0.57±0.95	0.222	0.22±0.36	0.52±0.93	0.456
Neutrophil count	32.60±29.67	18.37±30.42	0.265	10.81±15.40	33.96±32.22	0.024	3.72±5.89	34.98±30.86	< 0.001
NLR	1.08±1.33	0.26±0.38	0.033	0.24±0.37	1.00±1.28	0.033	0.09±0.17	1.01±1.24	0.005

Numerical data are expressed as means ± standard deviation. Bold P-values represent significant differences. BM, basement membrane; ELR, eosinophil-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

The roles of inflammation and tissue remodeling in the pathogenesis of CRS have been reported in numerous studies [3]. The inflammatory process and its effects may differ between CRSwNPs and CRSSNPs. CRSwNPs is characterized by a predominant type 2 inflam-

matory response mediated by T helper 2 cells and the release of IL-5, ECP, and eotaxin, as well as high local levels of IgE [10]. Eosinophil infiltrations along with downregulation of transforming growth factor (TGF-β) and a decreased number of regulatory T (Treg) cells are also

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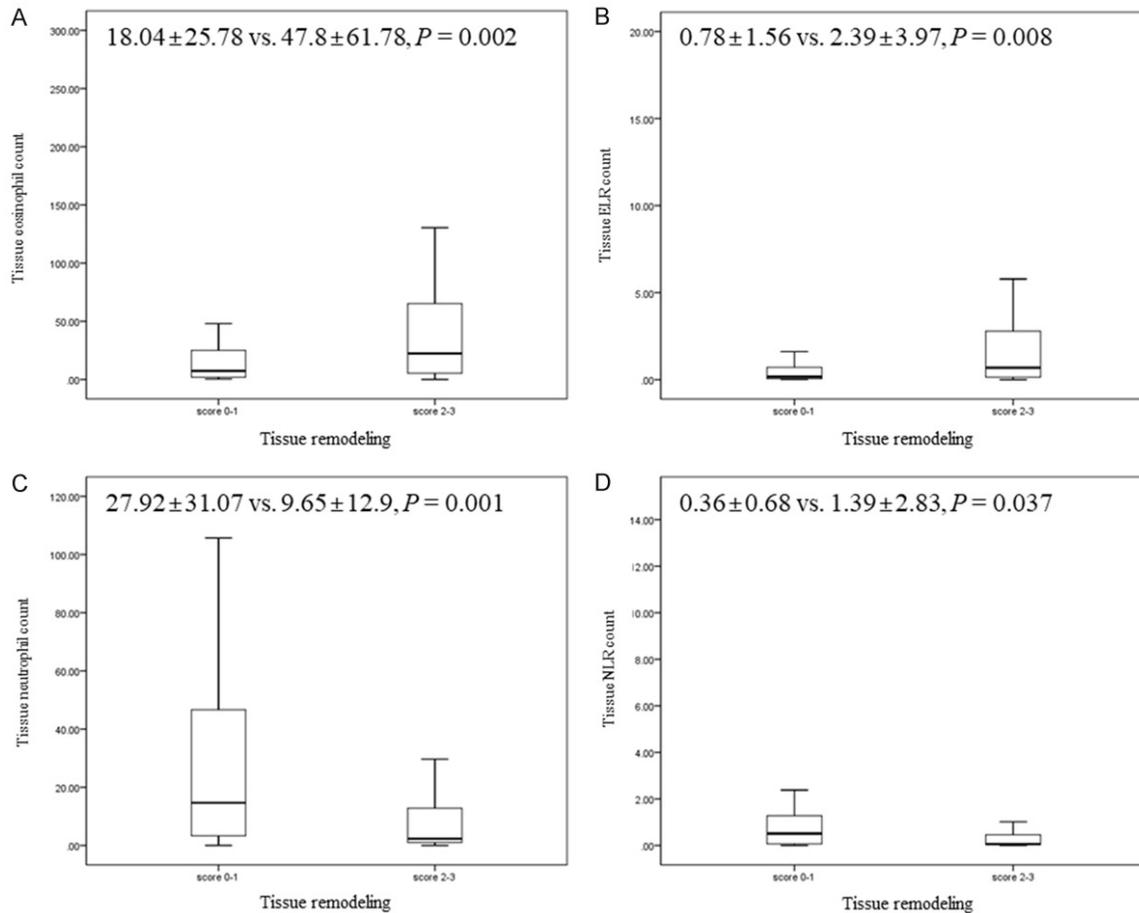


Figure 2. Comparisons of inflammatory marker levels according to the degree of tissue remodeling in chronic rhinosinusitis. (A and B) Tissue eosinophil count and eosinophil-to-lymphocytic ratio (ELR). (C and D) Tissue neutrophil count and neutrophil-to-lymphocytic ratio (NLR).

observed in CRSwNPs [3, 10]. These changes lead to increased tissue edema and inhibited collagen deposition in the extracellular matrix in CRSwNPs [11]. BM thickening is also correlated with the density of underlying eosinophils [12].

Conversely, in CRSsNPs, the inflammatory process is predominately mediated by T helper 1 cells [13]. Neutrophil infiltrations with upregulation of TGF- β and increased Treg cells result in increased collagen deposition and fibrosis formation in CRSsNPs [2]. In agreement with previous findings, stromal edema and BM thickening were more prominent in CRSwNPs than CRSsNPs in the present study. In addition, stromal fibrosis was more common in CRSsNPs than CRSwNPs but without statistical significance. Subgroup analysis also showed that tissue eosinophilia and ELR, but not tissue neu-

trophilia or NLR, were associated with histologic changes in CRSwNPs, indicating that Th2-type eosinophilic inflammation is more dominant in CRSwNPs.

Histologic changes such as stromal edema, stromal fibrosis, BM thickening, and squamous metaplasia are aspects of tissue remodeling, a dynamic process resulting in extracellular matrix production and degradation [10]. Inflammation does not always result in tissue remodeling; however, these two processes are intricately related [9]. Among inflammatory cells, eosinophils are the main effector cells in the inflammation and remodeling process [9]. In the present study, a higher tissue eosinophil count and ELR were observed in patients with two or more histologic changes compared with no or one histologic change, indicating that eosinophilic inflammation is the primary pro-

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cess in tissue remodeling [9]. In contrast, patients with only one or no histologic change had a higher neutrophil count and NLR. Because neutrophils are the first responders among inflammatory cells, the tissue neutrophil count and NLR might be decreased in chronic diseases such as CRS with tissue remodeling. Remodeling can also be observed in the non-eosinophilic type of inflammation, indicating that complex mechanisms other than those involving eosinophils are involved in tissue remodeling [14].

The role of tissue eosinophilia as a marker predicting CRS recurrence has been evaluated previously [15]. Patients with greater tissue eosinophilia had a greater risk of recurrence and more unsatisfactory treatment outcomes after sinus surgery [15]. However, neither a clear definition of, nor diagnostic criteria for, eosinophilic CRS has been established. In a recent meta-analysis, > 55 eosinophils per high power field was suggested as the cutoff eosinophil count for eosinophilic CRS [5]. However, the diagnosis of eosinophilic CRS can differ depending on the high-power fields selected by investigators when counting eosinophils. In addition, paraffin block sectioning can also affect the extent and severity of histologic changes.

To compensate for these shortcomings, inflammatory markers such as the ELR could be considered. The roles of inflammatory markers, including the ELR and NLR, have been investigated in various diseases [16-18]. These markers can be obtained not only from tissue but also from peripheral blood easily. A prognostic role of inflammatory markers in predicting CRS recurrence has been suggested [16]. In a previous study, the serum NLR was identified as an independent risk factor for CRS recurrence after sinus surgery [17]. Other studies showed that the serum NLR, ELR, and basophil-to-lymphocyte ratio were higher in recurrent CRS, but the results were heterogeneous among CRS sub-cohorts [16]. In addition to their role as a prognostic marker, serum inflammatory cells are closely associated with tissue inflammatory cells, especially eosinophils [19]. However, in the present study, tissue inflammatory markers were correlated with histologic changes, whereas serum inflammatory markers were not, except for a relationship between the serum

eosinophil count and BM thickening, regardless of the presence of nasal polyps. Our results showed that the serum inflammatory markers were not correlated with histologic changes irrespective of the CRS phenotype, indicating that serum inflammatory markers may not always represent histologic changes in CRS. Tissue inflammatory markers appear more to be specific and representative markers of disease extent compared with peripheral markers, which may suggest that circulating inflammatory cells are in a pre-activation state before their extravasation and migration to the tissue [20].

The present study had several limitations. First, clinical aspects such as disease extent and treatment outcomes were not evaluated. Second, a histologic assessment was made by only one pathologist; the adoption of more diverse tissue remodeling markers might be more helpful to elucidate the relationship between tissue remodeling and inflammation. Third, the histologic changes were dichotomously classified as present or absent. Further stratification of the changes into multiple grades might enable additional analyses [21].

In conclusion, our data showed that tissue inflammatory markers were correlated with histologic changes in CRS. In contrast, serum inflammatory markers showed limited ability to predict tissue remodeling. Mainly high levels of tissue eosinophilic and low levels of tissue neutrophilic markers were associated with tissue remodeling in CRS. These findings indicate the feasibility of tissue remodeling parameters as prognostic markers for CRS, in addition to conventional tissue eosinophilia.

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Disclosure of conflict of interest

None.

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