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Chronic Rhinosinusitis with Nasal Polyps in Older Adults: Clinical Presentation, Pathophysiology, and Comorbidity

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Abstract

Purpose of Review Chronic rhinosinusitis and nasal polyps (CRSwNP) is a common condition that significantly affects patients' life. This work aims to provide an up-to-date overview of CRSwNP in older adults, focusing on its aging-related clinical presentations, pathophysiology, and comorbidity associations including asthma.

Recent Findings Recent large population-based studies using nasal endoscopy have shown that CRSwNP is a mostly late-onset disease. Age-related changes in physiologic functions, including nasal epithelial barrier dysfunction, may underlie the incidence and different clinical presentations of CRSwNP in older adults. However, there is still a paucity of evidence on the effect of aging on phenotypes and endotypes of CRSwNP. Meanwhile, late-onset asthma is a major comorbid condition in patients with CRSwNP; they frequently present with type 2 inflammatory signatures that are refractory to conventional treatments when they are comorbid. However, as they are more commonly non-atopic, causative factors other than classical atopic sensitization, such as *Staphylococcus aureus* specific IgE sensitization, are suggested to drive the type 2 inflammation. There are additional comorbidity associations in older patients with CRSwNP, including those with chronic otitis media and head and neck malignancy.

Summary Age is a major determinant for the incidence and clinical presentations of CRSwNP. Given the heterogeneity in phenotypes and endotypes, longitudinal investigations are warranted to elucidate the effects of aging on CRSwNP.

Keywords Chronic rhinosinusitis · Nasal polyps · Asthma · Comorbidity · Aging

Introduction

Chronic rhinosinusitis (CRS) is one of the main chronic conditions in adults, affecting about 10% of the general population [1]. It is defined as chronic inflammation of the nose and paranasal sinuses, characterized by the presence of two or more of the following symptoms for more than 12 weeks: nasal discharge, nasal congestion or obstruction, facial pain or pressure, and reduction or loss of smell [2]. It significantly affects patients' quality of life, impairing their work productivity and social life [3]. A previous study using the 36-item Short-Form Health Survey reported that the effect of CRS on bodily pain and social functioning were comparable with or greater than that of other chronic diseases such as congestive heart failure, angina pectoris, chronic obstructive pulmonary diseases, and chronic back pain [4].

CRS is classified into two major subgroups based on endoscopy or computed tomography (CT) findings: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) [2]. Nasal polyps are inflammatory outgrowths of sinonasal tissues. They are usually benign but may cause severe nasal obstruction and reduction or loss of smell [5], and are frequently comorbid with severe asthma [1].

Of note, CRSwNP is a late-onset disease. A review of medical records of 4986 patients with asthma and rhinitis visiting an allergy clinic in the USA showed that the frequency of nasal polyps was significantly higher in patients older than

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40 years [6]. The Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2012—a nationwide general population survey wherein nasal endoscopy was routinely performed for all randomly recruited adult participants—found that the prevalence of nasal polyps increased with age in adults, being the highest in older adults (≥ 60 years of age) (Fig. 1a; unpublished). CRSwNP is also significantly associated with late-onset asthma [7•]. Given the trends of global population aging [8], its disease burden is expected to increase further in the near future. The present review aims to provide an up-to-date overview of CRSwNP in older adults, focusing on its aging-related clinical presentations and comorbidity associations including asthma.

Age-Related Epidemiology of CRSwNP

Smoking is a major risk factor for the prevalence of CRS overall. In a questionnaire-based study conducted by the Global Allergy and Asthma European Network (GA^{2}LEN), the prevalence of CRS according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EP^{3}OS) criteria was found to be 10.9% (range 6.9–27.1%) in European general adult populations [9]. CRS was significantly more prevalent in smokers than in non-smokers, but its prevalence was inversely associated with age (vs. 15–24 years as the reference group; for 65–74 years, odds ratio [OR] 0.64; 95% confidence interval [95% CI] 0.56–0.73) [9]. However, Chinese study performed using the same EP^{3}OS criteria found that older age (≥ 60 years) was not significantly associated with CRS prevalence (vs. 0–14 years as the reference group; OR 1.27; 95% CI 0.89–1.82) [10]. In a Korean population survey, the prevalence of overall CRS did not show a correlation with age (Fig. 1a) [7•]. These discrepancies in age relationships may be attributed to the different relationships of CRSsNP and CRSwNP with age.

Aging is however a major determinant of CRSwNP. The study by Johansson et al. was the first to report the prevalence of nasal polyps in general adult populations with objective confirmation of diagnosis using nasal endoscopy

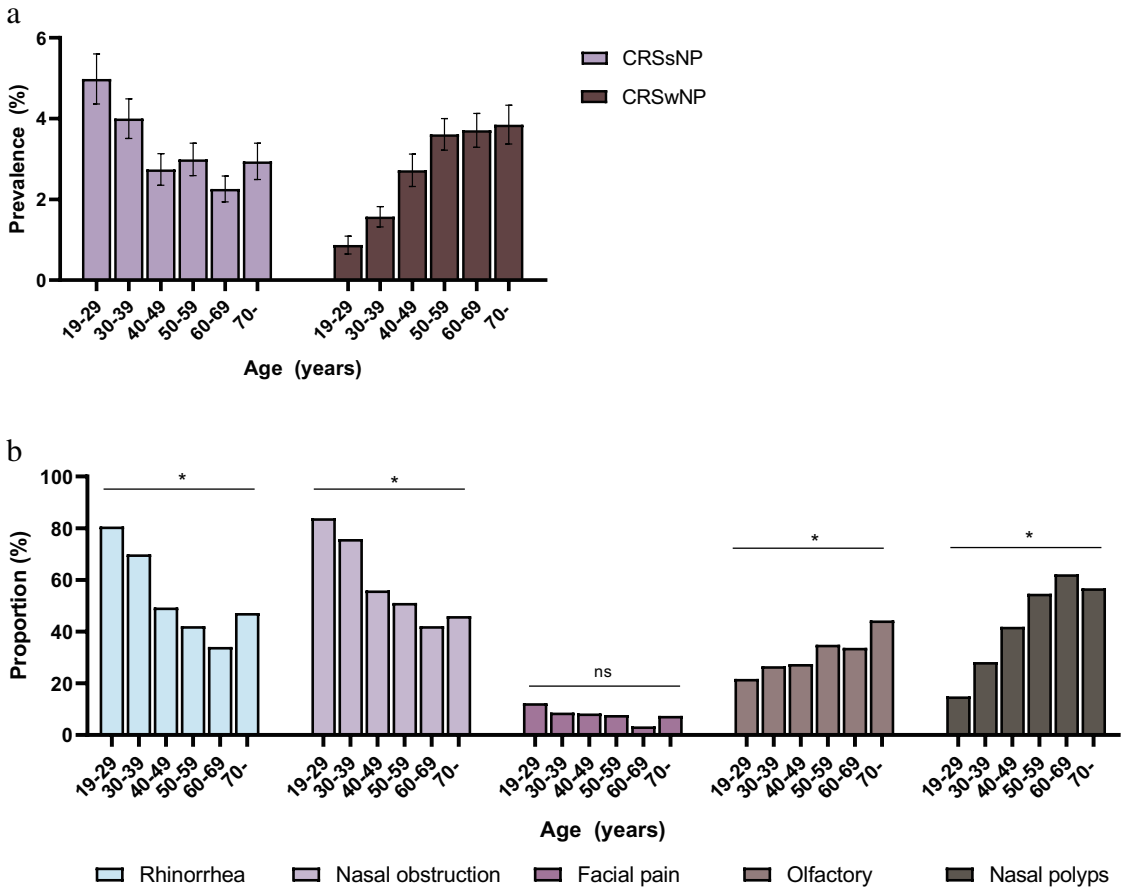

Fig. 1 **a** Age-related prevalence of chronic rhinosinusitis (CRS) with or without nasal polyps in a nationwide Korean population study. **b** Proportion of nasal symptoms with or without polyps among patients with CRS. Results from the 2010–2012 Korean National Health and Nutrition Examination Survey database analyses

[11]. In a random sample of 1900 adults in Skövde, Sweden, in 2000, the prevalence of nasal polyps was estimated to be 2.7% (95% CI 1.9–3.5%). The authors described the predicted probability of nasal polyps using a logistic regression model and demonstrated that this nasal condition is more prevalent in older adults, particularly among males and those with asthma [11]. These relationships with male sex and aging were also found in the KNHANES 2008–2012 analysis [12•]. The prevalence of CRSwNP was 2.6%, and it was significantly higher among older males and those with asthma. Multivariate logistic regression analyses showed that the male sex association was independent of smoking history [12•]. Similar demographic patterns were reported in an electronic health record data analysis of 446,480 Geisinger Clinic primary care patients in the USA [13] and in the GA^{2}LEN cohort of CRS patients in Europe [14]. However, the reasons underlying the aging-related incidence of CRSwNP are unknown. Smoking is an unlikely explanation for this relationship, as it was not independently associated with CRSwNP [12•]. Similarly, a history of allergic rhinitis, which is a usually childhood-onset disease, also shows no significant associations with CRSwNP [7•]. Indeed, there are different inflammatory endotypes of CRSwNP [15], and thus, the biological pathways underlying nasal polyp development in normal nasal mucosa are likely complex.

Pathophysiology of CRSwNP in Older Adults

CRSwNP is a heterogeneous entity, probably resulting from complex interplays among environment, host, and microbial factors [16, 17]. The pathophysiology is likely to be more complex in older adults, as it would include age-related changes in biologic functions. Physiologically, several aging-related anatomical and functional changes—such as decreased ciliary beat frequency, nasal mucosal atrophy, decreased nasal vasculature, and decreased nasal mucous secretion—may occur in the nasal mucosa [18]. Decreased ciliary beat frequency and clearance as well as thinning and dryness of the mucosa may lead to the stasis of thick mucus, followed by poor removal of external irritants [18].

Hereditary factors may underlie the incidence of nasal polyps, as the familial aggregation of CRSwNP has been reported [19–23]. In a population database study involving 1638 patients with CRSwNP diagnosed between 1996 and 2011 in Utah, the USA, first-degree relatives of CRSwNP patients had a 4.1-fold higher risk of having nasal polyps than did controls [23]. In a study of 418 CRSwNP patients in China, 17.4% of participants reported a family history of nasal polyps and had an earlier disease onset than patients without a family history (27.7 ± 12.7 vs. 32.7 ± 14.6; $p < 0.05$) [22]. However, it is unknown whether hereditary factors contribute to the development of nasal polyps in older adults and which specific genetic factors are involved in.

Innate and adaptive immune responses may be impaired in older adults, which also likely increase susceptibility to infection and bacterial colonization. Cho et al. reported a significant age-related decline in the levels of S100A8/9, members of the epidermal differentiation complex, in nasal lavage samples from both CRS patients and normal controls, suggesting that nasal epithelial barrier dysfunction is likely an aging-related biological change [24, 25•]. In a study of middle meatus swabs from 28 healthy participants without rhinosinusitis, advanced age was found to be associated with the microbiome composition at the phylum level. In particular, older participants had lower levels of *Actinobacteria* but concomitantly greater abundance of *Fusobacteria* and *Staphylococcus aureus* than younger participants [26]. *S. aureus* commonly colonizes the nasal mucosa of CRSwNP patients (up to 73.2%, as measured by nasal swab cultures) [27], and colonization is positively associated with local levels of immunoglobulin E (IgE) and eosinophils in nasal polyp tissues [28].

Age-Related Immunological Phenotypes of CRSwNP

The immunological phenotypes of CRSwNP vary geographically [29]. CRSwNP is commonly characterized by high Th2 cytokine levels and eosinophilic inflammation in European patients, whereas non-eosinophilic CRSwNP is more prevalent in Asian patients [30, 31, 32•, 33•]. Longitudinal comparison studies have reported that eosinophilic CRSwNP is becoming more frequent in Asian patients [34–36], suggesting important roles of environmental or acquired factors in developing immunological phenotypes. However, it is still unclear whether age influences immunological phenotypes. As the studies on CRSwNP in relation to aging are very limited, studies on CRS (including CRSwNP) have also been discussed herein.

A retrospective review of 252 patients with CRS visiting a specialist clinic in the USA showed no significant correlation between age and eosinophil count in nasal polyp tissues; however, a significant inverse correlation between age and eosinophil cationic protein levels in nasal lavage fluid was observed among patients with CRSwNP ($r = -0.57$, $p < 0.001$) [24]. Also, the proportion of eosinophilic histologic type did not differ between older and younger patients with CRSwNP in two different patient samples [34, 37]. Meanwhile, in a study of Korean

patients with non-eosinophilic CRSwNP, age showed inverse correlations with neutrophilic infiltration and levels of neutrophil-associated cytokines such as IL-17A and IL-23 in nasal polyp tissues. Further, the age-related decreases in levels of neutrophilic markers showed correlations with better post-operative endoscopic scores [38•]. However, in a study of 147 CRS patients undergoing endoscopic sinus surgery (ESS) in the USA, older patients had significantly more tissue neutrophils and bacterial culture-positive purulence than younger patients, and age was positively correlated with mucus levels of pro-inflammatory cytokines such as IL-1ß, IL-6, IL-8, and TNF-α [39••]. Collectively, the findings are inconsistent so far, and it is unclear whether age can have major influence on the immunological phenotypes of CRSwNP. However, the lack of consistency among cross-sectional studies suggests possible complex age relationships, which is likely to be non-linear, and indicates the need for longitudinal investigations to elucidate aging-related changes in inflammatory phenotypes of CRSwNP.

Age-Related Clinical Characteristics of CRSwNP

Using the KNHANES 2010–2012 database, we examined age-related differences in the pattern of cardinal symptoms and the presence of nasal polyps among CRS patients from the general population. Interestingly, contrasting patterns were observed between age groups—older patients reported more loss of smell, but less rhinorrhea or nasal obstruction, than did younger patients (Fig. 1b; unpublished data). These findings suggest that the clinical presentation of CRS in older patients is likely to be less typical than in younger patients. Aging-related anatomical and physiological changes—such as nasal mucosal atrophy, decreased nasal vasculature, or decreased nasal mucus secretion [18]—may underlie the age-related differences in nasal symptom profiles.

Studies based on data from specialist clinics have reported age-related differences in the clinical characteristics of CRSwNP, including the post-operative prognosis. Brescia et al. compared the clinical characteristics and post-operative clinical courses of 43 older patients and 71 young patients with CRSwNP after ESS [37, 40]. At baseline, there was no significant difference in the prevalence of asthma, aspirin-exacerbated respiratory diseases, and blood or nasal polyp tissue eosinophilia between the two age groups [40]. However, the recurrence rate of nasal polyps (defined as endoscopic evidence of at least grade I polyposis during a follow-up of approximately 2 years) was lower in older patients than in younger patients (11.6% vs. 28.2%; $p = 0.05$) [37]. Similar findings were observed in patient studies from Korea, where non-eosinophilic nasal polyposis is a predominant pathologic subtype [38•]. Kim and colleagues found that older patients with CRSwNP had significantly lower pre-operative Lund-Mackay CT scores and better post-operative endoscopic scores at 12 months than did younger patients [38•]. In another Korean study of 60 CRSwNP patients undergoing ESS, post-operative endoscopic scores at 6 months were better in older patients than in younger ones [41]. A small study of 20 patients undergoing ESS for CRSwNP suggested that a lower cellular proliferative ability, measured and evaluated based on proliferating cell nuclear antigen and Ki67 reactivity in tissues, might be related to better surgical outcomes in older patients [42].

Late-Onset Asthma in Patients with CRSwNP

Asthma is a major comorbid condition in patients with CRSwNP (up to 60%) [32•, 43]. This is particularly relevant clinically because in such cases, asthma frequently shows late onset and is difficult to treat [1]. In the KNHANES 2010–2012 analysis, unlike in individuals without CRS or with CRSsNP, age at asthma onset was typically above 40 years in patients with CRSwNP [7•]. It is still unknown whether CRSwNP predisposes to asthma or vice versa. Meanwhile, CRSwNP comorbidity is closely related to asthma severity in older patients with asthma [44].

Despite consistently reported associations between CRSwNP and asthma in large adult population studies [6, 7•, 11, 13, 14], the mechanisms underlying these associations are not fully understood. However, interestingly, CRSwNP and asthma frequently present with type 2 inflammatory signatures when they are comorbid. In a cluster analysis of CRS patients based on immunological biomarkers, 10 clusters with distinct cytokine patterns were identified, correlating with clinical phenotypes in terms of nasal polyps and asthma comorbidity [32•]. Notably, the high IL-5 clusters showed increased local levels of total IgE and staphylococcal enterotoxin-specific IgE (SE-IgE) in nasal tissues and also a higher frequency of nasal polyps and asthma [32•]. Asthma comorbidity is more frequent in refractory CRSwNP patients with type 2 high inflammatory signature than in those with non-refractory or non-eosinophilic CRSwNP [45]. Meanwhile, in a cohort study of older patients with late-onset asthma, CRSwNP was found to be closely related to severe eosinophilic asthma and elevated SE-IgE serum levels [46•].

As patients with CRSwNP or late-onset asthma are frequently non-atopic, causative factors other than inhalant allergen IgE sensitization are postulated to drive the type 2 inflammatory process. Unlike inhalant IgE sensitization, the SE-IgE sensitization rate may increase with aging or remain high in older adults and is positively associated with asthma prevalence in general populations [47•, 48•]. In a recent nested case-control study from the 20-year Epidemiological study on the Genetics and Environment of Asthma-EGEA cohort, SE-IgE sensitization was also significantly associated with asthma severity

(adjusted OR 2.69; 95% CI 1.18–6.15) and asthma exacerbations (adjusted OR 4.59; 95% CI 1.40–15.07) 10–20 years later [49]. As *S. aureus* is a frequent colonizer in the nasal mucosa and its colonization is positively associated with asthma in adults [27], the common associations of SE-IgE, an immunologic marker for host interactions, suggest that the bacterial exposure is one of important factor linking between CRSwNP and asthma. Meanwhile, as nasal colonization by *S. aureus* is only modestly associated with asthma [27, 50], certain host interactions would be key to developing SE-IgE sensitization and allergic inflammation. As SE-IgE sensitization is more common in smokers [48•], environmental irritant exposure, such as cigarette smoking, is postulated to have adjuvant effects.

Staphylococcus aureus can reside and proliferate within host cells in nasal polyp tissues, including epithelial cells and mast cells [51–53]. Importantly, *S. aureus* produces bacterial proteins that can initiate or exacerbate type 2 inflammation of the airways [54]. Staphylococcal serine protease–like proteins (Spls) are recently identified bacterial proteins that can induce type 2 inflammation in an IL-33-dependent manner [55•, 56••]. Asthma patients have significantly higher levels of IgE relative to Spls than do controls without asthma. Moreover, in mice, repeated intratracheal administration of SplD without an adjuvant leads to eosinophilic lung inflammation and SplD-specific IgE sensitization [56••], indicating potential key roles of Spls in the pathogeness of S. aureus-related airway diseases such as CRSwNP and asthma of late-onset.

Other Comorbidities in Patients with CRSwNP

Otitis media is another frequent comorbid condition in patients with CRS [57]. In a cross-sectional study of 80 patients with CRSwNP, chronic otitis media (COM) with effusion was found in 25% of the patients [58]. In the KNHANES 2009–2012 database analyses by Hong and colleagues, where COM was defined by otologic endoscopic findings of tympanic membrane perforation or cholesteatoma, the overall prevalence of COM was 3.6 ± 0.2% (95% CI 3.3–3.9%) and increased with age [59•]. COM was significantly associated with CRSwNP (vs. no CRS as the reference; adjusted OR 1.920; 95% CI 1.080–3.410) but not with CRSsNP (adjusted OR 1.504; 95% CI 0.608–3.718). Notably, the associations between CRSwNP and COM were significant in older adults (> 50 years) but not in younger adults (19–49 years) [59•].

Head and neck cancers are very rare, but their relative risks reportedly increase in older patients with CRS or nasal polyps. In recent analyses of the SEER-Medicare database containing 483,546 older adults (≥ 60 years) from the USA, CRS was found to be associated with the nasal cavity and paranasal sinus (NCPS) and nasopharyngeal cancers [60, 61]. In a nationwide population-based retrospective longitudinal cohort study of 453,892 patients with nasal polyps and 4,583,938 matched comparators from Korea (mean duration of follow-up 6.2 years), the incidence rate ratios of nasal polyps were 7.00 (95% CI 5.28–9.25) for NCPS cancer and 1.78 (95% CI 1.28–2.42) for nasopharyngeal cancer. However, the increased risks were only evident in older patients (≥ 50 years) [62•]. Given the regional and pathological heterogeneity of nasal polyps, further validation studies are warranted to confirm their relationship with these cancers. However, these findings suggest that further clinical attention might need to be paid to CRSwNP occurring at an advanced age.

Conclusion

CRSwNP is a common condition that significantly affects the patient's life. It may cause severe nasal symptoms and frequently co-exists with severe asthma. Notably, CRSwNP is a

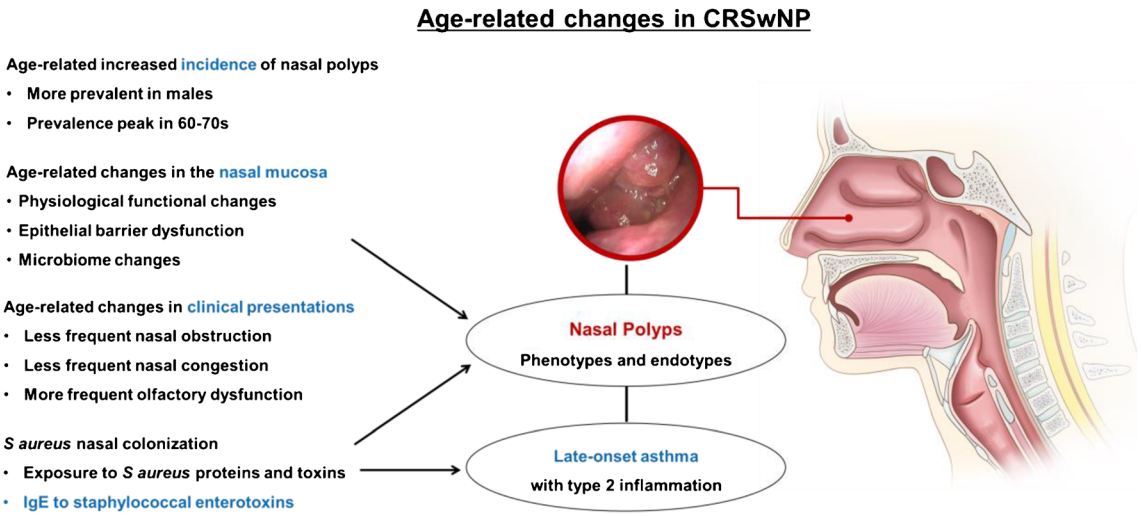

Fig. 2 Summary of age-related changes in epidemiology, clinical presentations, and pathophysiology of chronic rhinosinusitis with nasal polyps (CRSwNP)

mostly late-onset disease with different inflammatory endotypes. The pathophysiology is likely to be more complex in older adults, as it would include age-related changes in biologic functions (Fig. 2). Unlike younger patients, older patients with CRSwNP may present with less typical symptoms, with less frequent nasal obstruction or discharge. However, there is still a paucity of evidence on the effect of aging on phenotypes and endotypes of CRSwNP. Available evidence suggests that the effects are likely to be complex, as reflected by the discrepant findings between published cross-sectional studies. Thus, longitudinal investigations are warranted to understand the effects of aging. Meanwhile, late-onset asthma is a major comorbid condition in patients with CRSwNP and is frequently difficult to treat. Such patients may present with type 2 inflammatory signatures, and chronic repeated exposure to *S. aureus* and subsequent host immune responses may underlie these relationships. There are additional comorbidity associations in older patients with CRSwNP, including those with COM and malignancy. These findings collectively indicate the need for more comprehensive research and a clinical approach to CRSwNP in older adults.

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Compliance with Ethical Standards

Conflict of Interest Woo-Jung Song reports grants from MSD and Astra Zeneca, outside the submitted work. Ji-Hyang Lee, Ha-Kyeong Won, and Claus Bachert declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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