The role of TAS2R38 genotype in surgical outcomes and culturable bacteria in chronic rhinosinusitis with or without nasal polyps*

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Abstract

Background: Recent studies reported the relationship between genetic variations and TAS2R38, which is a bitter taste receptor expressed in the cilia of human sinonasal epithelial cells, among the predisposing factors playing role in immune response to upper respiratory tract bacterial infection. The present study aims to examine the relationship of TAS2R38 genotype with the active microorganism and the effect of genotype on the surgical outcomes among chronic rhinosinusitis patients.

Methodology: 34 patients undergoing endoscopic sinus surgery (ESS) for chronic rhinosinusitis with or without polyps (23 CRSwNP, 11 CRSsNP) and 30 patients undergoing septoplasty surgery for isolated nasal septum deviation were included. All the patients were genotyped for TAS2R38. Scoring was made using endoscopic Modified Lund-Kennedy and radiological Lund-Mackay systems preoperatively. Sino-Nasal Outcome Test with 22 items (SNOT-22) was implemented preoperatively and postoperatively. Nasal swab culture samples were taken intraoperatively from CRS patients and the active microorganism were isolated.

Results: In the TAS2R38 genotyping of the study group, PAV/PAV was found in 32.4% of patients, PAV/AVI in 47.1%, and AVI/AVI in 20.6%. In the control group, PAV/PAV was found in 26.7%, PAV/AVI in 36.7%, and AVI/AVI in 36.7%. In the study group, there was no statistically significant difference between the CRS and CRS subgroups in terms of TAS2R38 genotype distributions. The changes in patients' preoperative and postoperative SNOT-22 scores were similar between the genotypes. Proliferation was detected in culture in the whole AVI-AVI group, 81.8% of PAV-PAV group, and 56.3% of PAV-AVI group but the difference was not found to be statistically significant. The proliferation level of *Staphylococcus epidermidis* by TAS2R38 genotype was found to be statistically significantly higher among patients, who had AVI-AVI genotype, in CRSwNP.

Conclusions: We did not find a statistically significant relationship between the TAS2R38 genotype and CRS subtype, sinonasal bacterial infection risk increase and surgical success rate in CRS patients. Long-term and large-scale studies are needed, which are to be carried out by individual genotyping and sequencing to provide more information on the effects of these genetic variants.

Key words: culture, endoscopic surgical procedure, sinusitis, TAS2R38 protein

Introduction

High prevalence of chronic rhinosinusitis (CRS) in the general population places a significant burden on the businesses and healthcare services since it decreases the quality of life [(1,2)].
Even though a remarkable recovery is achieved in most of the patients after ESS, CRS symptoms are still observed in 25%. It is very difficult to estimate in which patients the symptoms will be permanent. So, if biomarkers that correlate with surgical success rates could be defined, they can be used in patients' postoperative treatment selection and planning [(3)].

In recent years, it was proposed that the genetic polymorphisms of bitter taste receptors contribute to CRS. These receptors are connected to G protein and, when activated, they create an

effect potential triggering the release of calcium within the cell and the perception of taste. T2R38, which is located on chromosome 7q, plays a special role in the perception of the taste of phenylthiocarbamide (PTC), which is one of the best characterized genetic features [2]. It was reported that T2R38, a bitter taste receptor, was expressed in ciliated cells in the human upper respiratory tract. It was also determined that T2R38 is stimulated by gram-negative bacteria resulting in the production of nitric oxide (NO). In airway, NO increases the mucociliary clearance and directly kills the bacteria. Receptor activity depends on three common single-nucleotide polymorphisms in TAS2R38 gene. There are two T2R38 proteins based on the amino acid residues at positions 49, 262, and 296. The functional allele of this receptor includes PAV, whereas the non-functional allele includes AVI. Thus, the active haplotype is named PAV, whereas the inactive haplotype is named AVI [4]. These haplotypes determine the level of PTC taste perception as super taste (PAV/PAV), moderate taste (PAV/AVI), and no taste (AVI/AVI). In previous studies, it was reported that, in comparison to the other two genotypes, the super taste genotype responded significantly more to pseudomonal quorum sensing molecules [5].

It is not known why some individuals are more prone to CRS development and why some patients showed persistent disease or bacterial inflammation even though some others responded well to treatment. In the present study, it was aimed to examine the relationship of TAS2R38 genotype with active microorganism and this genotype's effect on surgical outcomes in a Turkish cohort of patients.

Materials and methods

Study and control groups

The patients affected by CRS with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP), as defined by the European guidelines, and referred to the outpatient clinic for routine follow-up were included in the present study [1]. While examining the patients, a detailed anamnesis was obtained and main demographic data, previous history of ESS, allergic rhinitis, asthma, and aspirin allergy were questioned. The topical steroid and antibiotic treatments were ceased at least 4 weeks prior to the surgery. Turkish version of SNOT-22 was implemented with all the patients preoperatively and on postoperative 180th day [6]. The results obtained from preoperative and postoperative endoscopic nasal examinations of patients were graded using the Modified Lund-Kennedy grading system. The results achieved in preoperative paranasal sinus CT were rated using Lund Mackay radiological grading system. Using an intraoperative endoscope, nasal swab samples of CRS patients were taken by making use of sterile cotton swab sticks on both OMC sites. As the postoperative standard treatment, all patients were started on nasal rinse within postoperative 24 hours (3 times a day for 4 weeks), antibiotherapy within the postoperative 1st week, and the intranasal steroid on the postoperative 10th day. The control group consisted of patients, for whom a surgical intervention was planned due to isolated nasal septum deviation and who accepted to participate in the study. The patients aged younger than 18 years and older than 75 years, having a history of autoimmune disease, immunodeficiency, ciliary disorder, and malignity, and having used steroids orally in the last 3 months were not included.

Ethics committee approval was obtained from a local ethics committee (11/04/2019-11/13). All participants provided informed consent to use their samples for research purposes. Research was carried out in compliance with the Helsinki Declaration.

Tissue sampling and DNA extraction

Polyp tissue samples were taken from CRSwNP patients undergoing ESS under general anesthesia and mucosal tissue samples from uncinectomy zone of CRSsNP patients, while venous blood samples were taken from all the patients for genetic analysis.

Genomic DNAs of participating patients were isolated from tissues by using GeneAll Exgene Cell SV mini 250 preps kit K106-152. DNA isolation from blood was performed using Invitrogen PureLink Genomic DNA kit K1820-02. TAS2R38 genotype was determined as described [7].

Microbiological analysis

All the specimens were subjected to aerobic and anaerobic culture and gram-staining tests. The proliferation in plates with completed incubation was determined using VITEK® MS (BioMérieux, France) MALDI-TOF (Matrix-assisted laser desorption ionization time of flight mass spectrometry) device. Antibiotic sensitivity of identified bacteria was examined using Vitek-2 (BioMérieux, France) device.

Statistical analysis

All the statistical analyses were performed using IBM SPSS 23.0 package software (IBM Corp., Armonk, NY, USA). Normality assumption was tested using the Shapiro Wilk test. The relationships between categorical variables were analyzed using Fisher's Exact Test or Pearson's Chi-Square test. The difference between the measurement results of two groups was analyzed using Student's t-test. The comparisons between three or more groups were performed using ANOVA test. However, the comparisons between two groups were performed using Tukey's HSD test when the variance homogeneity was achieved and Dunnet T3 test when the variance homogeneity was not achieved. Statistical significance was accepted as $p<0.05$.

Table 1. Demographic characteristics and distribution of genotypes in study and control groups.

Variables	CRSwNP (n=23)	CRSsNP (n=11)	Control (n=30)	p
Age	39.4 ± 13.2	37.2 ± 14.7	35 ± 12.2	0.474
Gender				
Male	20 (87)	6 (54.5)	14 (46.7)	0.009
Female	3 (13)	5 (45.5)	16 (53.3)	
TAS2R38				
PAV-PAV	8 (34.8)	3 (27.3)	8 (26.7)	0.688
PAV-AVI	10 (43.5)	6 (54.5)	11 (36.7)	
AVI-AVI	5 (21.7)	2 (18.2)	11 (36.7)	

Results are expressed as mean ± SD or n (%). ANOVA, Pearson's Chi-Square test, and Fisher's Exact test.

Table 2. Patient characteristics by genotype.

Variables	PAV-PAV (n=11)	PAV-AVI (n=16)	AVI-AVI (n=7)	P
Primary surgery	8(72.7)	12(75)	4(57.1)	0.788
Allergic rhinitis	8(72.7)	11(68.8)	6(85.7)	0.880
Asthma	2(18.2)	5(31.3)	3(42.9)	0.490
Aspirin Allergy	2(18.2)	1(6.3)	1(14.3)	0.658
Preoperative SNOT-22 total score	44.2 ± 23.9	42.4 ± 12.4	43.4 ± 12.6	0.966
Postoperative SNOT-22 total score	10.3 ± 7	13.3 ± 10.5	8 ± 6.4	0.382
Modified Lund-Kennedy score	8.3 ± 2.2	8 ± 2	8.1 ± 2.3	0.949
Lund-Mackay score	16.9 ± 8	15.4 ± 6.1	16.9 ± 6.5	0.814
Bacterial growth	9(81.8)	9(56.3)	7(100)	0.063
Multiple growth	1(9.1)	2(12.5)	3(42.9)	0.213

Results are expressed as mean ± SD or n (%). ANOVA. Fisher's Exact test.

Results

The present study included 64 patients in total. Of these volunteers, 34 (53.1%) were assigned to the study group and 30 (46.9%) to the control group. In the study group, there were 23 (67.6%) CRSwNP and 11 (32.4%) CRSsNP patients. Demographic characteristics and genotype distributions in study and control groups are presented in Table 1.

Of the patients in the study group, 32.4% were found to have PAV/PAV (n=11), 47.1% to have PAV/AVI (n=16), and 20.6% to have AVI/AVI (n=7). In the control group, however, 26.7% of patients were found to have PAV/PAV (n=8), 36.7% to have PAV/AVI (n=11), and 36% to have AVI/AVI (n=11). It was found that there was no statistically significant difference between the study and control groups in terms of the distribution of TAS2R38 genotypes (p=0.359). The characteristics of CRS patients by the genotype are presented in Table 2.

Among the CRS patients, proliferation in culture was detected in 100% of AVI-AVI group, in 81.8% of PAV-PAV group, and in 56.3% of PAV-AVI group. However, the difference was not statistically significant (p=0.063). Examining the microorganism proliferation by TAS2R38 genotype, it was determined that there was no statistically significant difference between the groups (p>0.05). Although the level of proliferation of gram-positive microorganisms in patients with the AVI-AVI genotype (71.4%) was higher, the difference was not statistically significant (p=0.239) (Table 3). Given the numbers of microorganism proliferation by TAS2R38 genotype in CRS subtypes, the proliferation of *Staphylococcus epidermidis* in patients with AVI-AVI genotype in CRSwNP group was found to be statistically significantly higher (p=0.040).

The preoperative mean total SNOT-22 score of the study group was found to be 43.2 ± 16.5, while the mean total SNOT-22 score on the 6th postoperative month was 11.2 ± 8.8. The mean postoperative SNOT-22 score of CRSsNP group was determined to be higher, but the difference was found to be statistically insignificant (p=0.062).

The distribution of SNOT-22 in CRS patients by genotype was

Table 3. Microorganism isolated in CRS patients and the relationship with genotype.

Variables	PAV-PAV (n=11)	PAV-AVI (n=16)	AVI-AVI (n=7)	P
Streptococcus pneumonia	0 (0)	1 (6.3)	0 (0)	0.999
Finegoldia magna	2 (18.2)	0 (0)	0 (0)	0.135
Staphylococcus aureus	2 (18.2)	2 (12.5)	2 (28.6)	0.735
Enterobacter aerogenes	1 (9.1)	2 (12.5)	2 (28.6)	0.568
Citrobacter koseri	0 (0)	2 (12.5)	1 (14.3)	0.426
Aspergillus fumigatus	0 (0)	0 (0)	1 (14.3)	0.206
Staphylococcus epidermidis	1 (9.1)	1 (6.3)	3 (42.9)	0.105
Enterobacter cloacae complex	1 (9.1)	0 (0)	0 (0)	0.529
Morganella morganii	1 (9.1)	0 (0)	0 (0)	0.529
Enterobacter asburiae	1 (9.1)	0 (0)	0 (0)	0.529
Serratia marcescens	1 (9.1)	0 (0)	0 (0)	0.529
Klebsiella oxytoca	0 (0)	1 (6.3)	0 (0)	0.999
Staphylococcus haemolyticus	0 (0)	1 (6.3)	0 (0)	0.999
Acinetobacter	0 (0)	1 (6.3)	0 (0)	0.999
Fusarium	0 (0)	0 (0)	1 (14.3)	0.206
Gram-staining				
Gram-positive	5 (45.5)	5 (31.3)	5 (71.4)	0.239
Gram-negative	5 (45.5)	6 (37.5)	2 (28.6)	0.815

Results are expressed as mean ± SD or n (%). ANOVA. Fisher's Exact test.

Table 4. Comparison between preoperative and postoperative SNOT-22 mean scores of CRS patients.

	All patients (n=34)		CRSwNP (n=23)		CRSsNP (n=11)	
Variable	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
TAS2R38						
PAV-PAV	33.9 ± 24	0.674	34.1 ± 26	0.778	33.3 ± 22.9	0.657
PAV-AVI	29.1 ± 14.1		33.3 ± 11.9		22.2 ± 15.6	
AVI-AVI	35.4 ± 13.8		40.2 ± 13		23.5 ± 7.8	

Student's t-test.

found to be similar in preoperative PAV-PAV (44.2 ± 23.9), PAV-AVI (42.4 ± 12.4), and AVI-AVI (43.4 ± 12.6) genotypes (p=0.966). The postoperative 6th month distributions were found to be similar in PAV-PAV (10.3 ± 7), PAV-AVI (13.3 ± 10.5), and AVI-AVI (8 ± 6.4) genotypes (p=0.382) (Figure 1).

Comparing the preoperative and postoperative mean SNOT-22 score differences in CRS patients, it was found that there was no statistically significant difference between genotypes (p>0.05) (Table 4).

As a result of the full blood count of CRSwNP group, it was determined that the mean number of peripheral eosinophil (×10^3/µL) was 0.38 ± 0.18 and the mean percentage of peripheric eosinophil (%) was 4.9 ± 2.2.

Discussion

Although it has been reported that genetics might be a predisposing factor in the development of chronic rhinosinusitis, there are only few studies on this subject in the literature. A review of the current literature on genetics and CRS shows that the studies focus especially on the latest findings on cystic fibrosis transmembrane regulator, primary ciliary dyskinesia-related genes, and taste receptor T2R38. It was reported that T2R38 gene can be used in clinical environment by using a testable phenotype and it may play a role in determining the prognosis and management strategies for CRS patients [8].

To the best of our knowledge, the first study in literature, which was a pilot study carried out by Adappa et al. in 2013 on 28 CRS patients (13 CRSwNP; 15 CRSsNP), reported the genotype distri-

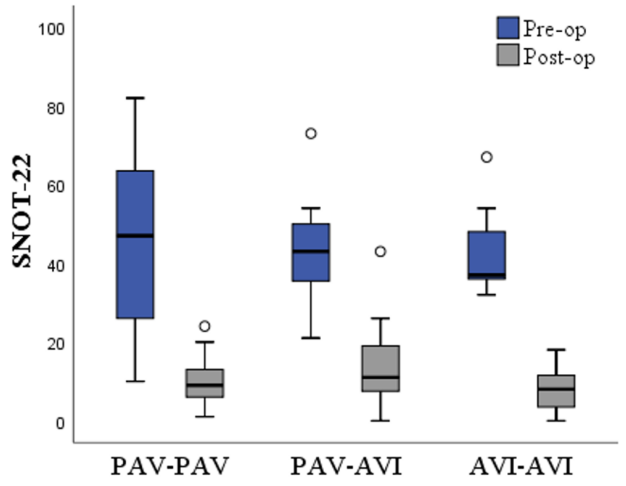

Figure 1. Preoperative and 6th postoperative month SNOT-22 distribution of CRS by genotype (Pre-op; preoperative, Post-op; postoperative).

bution as 3.6% PAV/PAV, 50% PAV/AVI, and 46% AVI/AVI. The authors found the ratio of PAV/PAV genotype among CRS patients to be lower than the other genotypes [9]. In their study carried out in year 2014 and comparing the genotype distribution of 70 CRS patients (38 CRSwNP; 32 CRSsNP) to that of 347 control participants, Adappa et al. determined that AVI/AVI genotype in CRS patients was significantly higher than expected and that of PAV/PAV genotype to be significantly lower than expected. They found no significant difference between the subgroups of CRS in terms of genotype distribution [10]. In their study comparing CRSwNP patients to a healthy population living in the same region, Cantone et al. found that AVI/AVI genotype had a higher prevalence [11]. Zborowska-Piskadło et al. immunohistochemically analyzed 42 patients, who had undergone nasal surgery, and, in comparison to the healthy controls, they determined the expression of TAS2R38 significantly to be higher in cell nuclei of CRS and CRSsNP patients than in cytoplasm [12]. Mfuna Endam et al. achieved results supporting the relationship between taste receptors and CRS. They showed that the TAS2R38 genotype was related with CRS [13]. Dżaman et al. stated that the distribution of TAS2R38 genotype varied by geographic region, race, and ethnical origin. They found correlation between the TAS2R38 genotype and CRS severity in Polish population. They also stated that AVI haplotype was an independent risk factor for CRS [14]. To the best of our knowledge, the present study is the first one carried out on this subject in Turkey. Given the current findings, it was determined that there was no statistically significant difference between study and control groups in terms of the distribution of TAS2R38 genotypes (p=0.359). Genotype distributions were found to be similar between CRS subgroups (n=23 CRSwNP, n=11 CRSsNP) and in comparison to control group (n=30) (p=0.688). Like the present results, Lin et al. compared the TAS2R38 genotype distributions of 652 CRS (426 CRSwNP; 226 CRSsNP) patients to those of 349 control participants and they found the distributions to be similar. The authors reported the genotype distributions of CRS subgroups to be like the control group [15]. Adappa et al., in their study carried out in 2016, reported no significant relationship between TAS2R38 genotype distribution of 207 patients (142 CRSwNP; 65 CRSsNP) and that of CRS subgroups [3]. Gallo et al., in their study carried out on 53 patients (36 CRSwNP and 17 CRSsNP) and 39 control group participants, found no relationship between any genotype and CRS [2]. In their study carried out on 25 CRS (11 CRSwNP; 14 CRSsNP) patients, Rom et al. also reported similar results regarding the distribution of genotype among CRS subgroups [16].

Significantly increased response of PAV/PAV genotype to the pseudomonal quorum sensing molecules suggests that it plays an important role in innate immune defense. Thus, it was considered that it can be protective against gram-negative sinonasal infections and relevant chronic inflammation. In their study, Adappa et al. showed that TAS2R38 genotype was significantly correlated to PTC taste sensitivity. They observed a significant correlation between in-vitro biofilm formation and PTC taste sensitivity among CRS and CRSsNP patients. The authors reported that PTC taste score predicted the in-vitro biofilm formation in CRSsNP patients. However, no significant result could be achieved by comparing the TAS2R38 genotype and in-vitro biofilm formation [4]. Examining the patients with gram-negative bacterial growth in sinonasal microbiological culture, Lee et al. found no PAV/PAV form. The authors considered that it may play role in respiratory defense against gram-negative bacteria including *Pseudomonas spp*. [7]. For 25 CRS patients whom they applied ESS, Rom et al. found a culturable organism in 48% (n=12) of the swab samples taken from patients' medial meatuses. They reported that 32% (n=8) of them were gram-positive and 2% (n=5) were gram-negative, while it was found by examining the microorganism species that 28% (n=7) of them were *Staphylococcus aureus* and 12% (n=3) were *Pseudomonas*. Genotype predicted the presence of culturable bacteria during the surgery. Proliferation in culture was detected in 58% of the PAV/AVI genotype and 42% of the AVI/AVI, whereas no proliferation in culture was found for the PAV/PAV genotype. The authors reported no relationship between gram-staining and cultured microorganisms [16]. In their study on the Italian population, Cantone et al. reported a negative correlation between the TAS2R38 genotype and gram-negative infections. In the study carried out with CRSwNP patients, of 63 patients with microbiological proliferation, gram-negative bacteria were found in 20 (32%), gram-positive bacteria in 36 (57%), and both in 22 (24%). The most isolated bacterium was *Staphylococcus epidermidis* (32%) followed by *S. aureus* with 24% and Enterobacteriaceae (*Klebsiella spp*., *Citrobacter koseri*, *Serratia marcescens*) with 35%. The authors associated the gram-negative infections in the

respiratory tract especially with the AVI haplotype [11].

In the present study carried out with CRS (CRSwNP and CRSsNP) patients, contrary to the literature, it was determined that proliferation was found in culture in all of the AVI-AVI group (100%), in 81.8% of PAV-PAV group, and 56.3% of PAV-AVI group but there was no statistically significant difference (p=0.063). Similarly, no significant difference was found in subgroups of CRS (p>0.05). *S. aureus* was isolated in 17.6% of patients, *Enterobacteriaceae spp*. in 38.1%, and *S. epidermidis* in 14.7%. In the present study, differing from the literature, the proliferation rates of gram-positive microorganisms in CRS (CRSwNP and CRSsNP) and CRSwNP patients were found to be higher among those having AVI-AVI genotype in comparison to the other genotypes but the difference was found to be statistically insignificant (p>0.05). Given the current findings, although the proliferation rate of gram-negative microorganisms was higher among CRSwNP patients having PAV/PAV genotype, the difference was not statistically significant (p=0.435). The finding that the rate of multiple microorganisms' proliferation in cultures of CRS patients and CRSwNP subgroup with AVI-AVI genotype was higher than in the other two genotypes may suggest the protectiveness of PAV haplotype. However, since there was limited number of patients in this study, no significant difference was found (p>0.05). In corroboration with the present findings, Gallo et al. reported no statistically significant results regarding the relationship between a specific genotype and an increase in the risk of sinonasal bacterial infection [2]. More comprehensive studies on this subject are needed.

Functional endoscopic sinus surgery became one of the most widely used methods, effectiveness of which in treatment of CRS was proven by data. Cases that are not treated sufficiently in primary surgery, comorbidities, and anatomic variation are considered to be the main factors playing a role in the failure of surgery [3]. Besides the risk factors, it is thought that, if the genetic factors and bioindicators having a correlation with success rates in surgery could be identified, then they can be used in directing the patients for better surgical outcomes. Adappa et al., in their study in year 2016, investigated the change in the preoperative SNOT-22 scores and postoperative 6th month scores in TAS2R38 genotype. While the recovery rate of CRS (CRSwNP and CRSsNP) patients with PAV/PAV genotype was 31 ± 25, the recovery rate of other patients (PAV/AVI, AVI/AVI, and other rare genotypes) was approx. 24 ± 22. Among the CRSwNP patients, the recovery rate of those having PAV/PAV genotype was found to be 29 ± 26 and 30 ± 20 for other patients. However, among the CRSsNP patients, the recovery rate in PAV/PAV genotype was 38 ± 21 and the rate in other genotypes was 12 ± 22. Besides that, the authors reported that the mean 6-month recovery rate of CRSsNP patients was significantly higher in those with a PAV/PAV genotype. They reported that the TAS2R38 genotype was correlated with surgical outcomes of CRSsNP patients. However, the authors reported no relationship between the change in SNOT-22 score and age, gender, previous ESS history, asthma, and aspirin allergy [3]. In the present study, in which TAS2R38 genotype and change between preoperative and postoperative SNOT-22 scores were examined, it was determined that, different from the study carried out by Adappa et al., no statistically significant difference was found between preoperative and postoperative SNOT-22 scores of CRSsNP patients, in addition to CRS and CRSwNP, by genotype (p>0.05).

The most important limitation of the present study is the small sample size. The reason for the small sample size was that the patients did not volunteer in participating in the study because of hesitation in coming to the hospital and the decrease in the number of elective surgeries during the COVID-19 pandemic. Another limiting factor was the need for longer follow-up periods for investigating the relationship between the genotype and recurrence because the patients had 6-month follow-up periods.

Conclusion

In literature, there are only few studies examining the relationship between the TAS2R38 genotype and chronic rhinosinusitis with and without polyps and reporting contradicting results.

In the present study, which we think is the first one in this geographic region, no relationship was found between CRS and TAS2R38 genotype and surgical success rates and isolated microorganisms. It is thought that comprehensive cohort studies are needed to use individual genotyping and sequencing for CRS cases and to provide more information about the effects of these genetic variants on CRS.

Authorship contribution

GY, HE and GOY: Study design, search, study selection, data collection, data analysis, drafting the article, and final approval. TK and NG: Data analysis. OEG, OTS and EAC: Revision, expert opinion. All authors approved the final version of the manuscript to be published.

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Conflict of interest

There was no conflict of interest.

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