Influence of Inhaled Drugs on Multidimensional Voice Quality of Asthma Patients: A Controlled Study

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SUMMARY: Objective. To investigate the voice quality in asthma patients treated with inhaled drugs (ID) through multidimensional voice quality assessment.

Methods. Consecutive patients with well-controlled asthma treated with ID were prospectively recruited from the otolaryngology offices of two private practice settings from August 2024 to April 2025. A control group of patients without ID treatment was composed of patients without ear, nose, and throat disorders. The voice quality of patients and controls was evaluated with the Voice Handicap Index (VHI), blinded perceptual GRBASI evaluation, maximum phonation time (MPT), and acoustic measurements. Laryngopharyngitis symptoms and findings were evaluated with the Reflux Symptom Score (RSS) and Reflux Sign Assessment (RSA). Laryngopharyngeal, nose, and eye dryness was evaluated with the total rating of eye, nasal, and dry-mouth (TREND) assessment.

Results. Thirty asthma patients with an inhaled corticosteroid treatment and 50 controls completed the evaluation. Asthma patients reported significantly higher VHI, GRBASI, RSS, and RSA compared to controls. MPT was significantly lower in asthmatics compared to controls. F0 standard deviation and percent shimmer were significantly higher in asthmatics versus controls. Grade of dysphonia and breathiness were significantly correlated with STD and percent shimmer.

Conclusion. ID users demonstrated impaired multidimensional subjective and objective voice quality evaluations compared to controls. Future controlled mechanistic studies are needed to better understand to relationship between ID and vocal fold function impairments.

Key Words: Laryngeal–Otolaryngology–Otorhinolaryngology–Voice–Corticosteroids–Vocal fold.

INTRODUCTION

The Global Asthma Report indicates that the global prevalence of asthma is 9.1% among children, 11.0% among adolescents, and 6.6% among adults in 2025,[1] with predictions indicating that the global age-standardized incidence rate will remain high from 2022 to 2050.[1] Most asthmatics are treated with inhaled drugs (ID), including corticosteroids, beta-2 agonists, and anticholinergics.[2] The deposit of some ID particles in the upper aerodigestive tract mucosa can result in adverse events manifesting as local symptoms and signs, including dryness and dysphonia.[3,4] Among them, inhaled corticosteroids, which are the most used ID in asthmatics, are associated with systemic and local adverse events in up to 81.5% of cases,[5] with a dose- and use-dependence according to meta-analyses.[6] A recent systematic review indicated that dysphonia may concern 5% to 58% of asthmatics treated with ID,[7] but it remains difficult to understand the pathophysiological mechanisms underlying the development of dysphonia due to the lack of studies considering standardized multidimensional voice quality assessments in ID users.[7]

The present study aimed to investigate voice quality in asthma patients treated with ID through a multidimensional voice quality assessment comparison with a control group.

MATERIALS AND METHODS

Setting and patients

Adult patients with controlled asthma disorders and daily intake of ID were prospectively recruited from the general otolaryngology consultation offices of two private practice settings from August 2024 to April 2025. All patients consulting the otolaryngologist (JRL) were interrogated on their list of medications, and those with ongoing daily ID treatment were invited to participate in the study. Inclusion criteria consisted of diagnosed asthma according to the global initiative for asthma (GINA) guidelines,[8] a stable, well-controlled asthma[8] for more than 3 months, daily use of ID, a recent lung assessment demonstrating control of the disease, and being native French speakers. A control group was composed from the same consultation including patients with no laryngopharyngeal, mouth, and nasal disorders; most of them having benign ear disorders such as ear wax or pruritus. Exclusion criteria for both groups included professional voice users, previous lung and laryngopharyngeal trauma, surgery, neoplasia, or radiotherapy, neurological and psychiatric illnesses, benign lesions of the vocal folds (eg, cyst, nodules, polyps), upper

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and lower respiratory tract infection within 4 weeks, chronic obstructive pulmonary disease, unstable asthma, alcohol consumption > 3 IU/daily, tobacco overuse (> 5 cigarettes/daily), use of medication affecting voice quality or dryness (ACE inhibitors, antihistamines, anticholinergics not for asthma), untreated hypothyroidism, and untreated allergic rhinitis.

Subjects consented to participate to the study. The ethic committee approved the study (Registre Voix, EpiCURA-2023).

Multidimensional voice quality evaluation

The multidimensional voice quality evaluation included patient-reported outcome questionnaires, perceptual evaluations, aerodynamic and acoustic measurements. Subjects completed the French version of the Voice Handicap Index (VHI).[9] The upper aerodigestive tract symptoms and findings associated with ID-induced laryngopharyngitis were evaluated with the reflux symptom score (RSS),[10] and the reflux sign assessment (RSA).[11] Moreover, laryngopharyngeal, mouth, nasal, and eye dryness was evaluated with the total rating of eye, nasal, and dry-mouth (TREND) questionnaire. TREND is a new patient-reported outcome questionnaire evaluating oral, laryngopharyngeal, nasal, and eye symptoms associated with dryness with a 6-point severity scale ranging from 0 (no symptom) to 5 (all times). The total TREND score ranges from 0 to 100 (severe head and neck mucosa dryness) (Figure 1).

Perceptual voice quality evaluations were carried out with the Grade of dysphonia, Roughness, Breathiness, Asthenia, Strain, Instability scale.[12] Two trained judges evaluated the GRBASI on recorded phonetic balanced text and sustained vowel /a/ in a blinded manner.

Videolaryngostroboscopy (Xion, Hamburg, Germany) was used to rate the ID-induced laryngopharyngitis with the reflux sign assessment (RSA).[11] Two authors rated the RSA in a blind manner.

The maximal phonation time (MPT) and the acoustic parameters were measured according to the 2024 European Laryngological Society and Union of European Phoniatricians recommendations.[13] Among acoustics, the following parameters were extracted from the sustained vowel /a/ with Praat (Belgium)[14]: standard deviation of fundamental frequency (STD), percent shimmer, percent jitter, harmonic-to-noise ratio (HNR), minimum and maximum sound pressure level (Xion).

Confounding conditions

According to the recommendations of the 2025 systematic review of ID vocal adverse events in asthmatics,[7] the presence of allergy in asthma patients was systematically recorded. Allergic patients and controls demonstrated controlled allergic rhinitis to reduce the risk of postnasal drip and related laryngopharyngeal symptoms and findings misattributed to ID use. Similarly, tobacco and alcohol consumption were recorded from all individuals. Subjects with uncontrolled allergic rhinitis, rhinosinusitis (with or without polyps) and high alcohol (> 3 IU/day), and tobacco (> 5 cigarettes/daily) use were excluded. Because laryngopharyngeal reflux disease (LPRD) is associated with nonspecific laryngitis symptoms and findings,[15]

Did you have the following symptoms in the last month?	Never	Rarely	Sometimes	Half of The time	Most of The time	All The time
Mouth and throat symptoms						
Dry throat	0	1	2	3	4	5
Dry/sticky throat mucus or throat clearing	0	1	2	3	4	5
Difficulty to swallow mucus	0	1	2	3	4	5
Foreign body sensation in the throat	0	1	2	3	4	5
Dry mouth	0	1	2	3	4	5
Thick or viscous saliva	0	1	2	3	4	5
Nasal symptoms						
Dry nose	0	1	2	3	4	5
Burning nose	0	1	2	3	4	5
Nasal crusts	0	1	2	3	4	5
Difficulty to breath with my nose	0	1	2	3	4	5
Postnasal thick discharge	0	1	2	3	4	5
Sensation of blocked ear/ear noise	0	1	2	3	4	5
Smell or taste disturbance	0	1	2	3	4	5
Eye symptoms						
Irritation, burning sensation, or stinging	0	1	2	3	4	5
Morning crusting or sensation of eyelids sticking together	0	1	2	3	4	5
Foreign body sensation (feeling of sand or grit in eyes)	0	1	2	3	4	5
Visual discomfort or light sensitivity	0	1	2	3	4	5
Redness of the eyes	0	1	2	3	4	5
Paradoxical tearing (excessive tearing despite dry eyes)	0	1	2	3	4	5
Blurred vision or decreased visual acuity	0	1	2	3	4	5

Total score:…...../100

FIGURE 1. The total rating of eye, nasal, and dry-mouth (TREND). The trend score is in process of validation. This score was developed to rate the dryness in mouth, laryngopharyngeal, nasal cavities, and eyes. The score ranges from 0 (no dryness) to 100 (severe dryness) with mild (10–30), moderate (31–60), and severe (> 61) dryness.

commonly found in ID-induced laryngopharyngitis, RSS and RSA were not used for detecting LPRD. Ideally, the 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing (HEMII-pH) is the gold standard to confirm or exclude LPRD.[16] However, given its cost and tolerance outcomes, the 24-hour HEMII-pH was not proposed in both asthmatic patients and controls. Only patients under treatment for LPRD were excluded.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 30.0; IBM Corp, Armonk, NY). Depending of the data, chi-square and Mann-Whitney *U* tests were used to compare demographic, clinical, and voice quality outcomes of asthmatic and controls. The interrater reliability was evaluated for the GRBASI and RSA evaluations, which were carried out in a blind manner by the two authors. A correlation analysis between acoustics and clinical findings was conducted with the Spearman correlation coefficient. The outcome association was considered as low, moderate, and strong for $k < 0.40$, 0.40–0.60, and $k > 0.60$, respectively. A level of significance of $P < 0.05$ was used.

RESULTS

A total of 30 asthmatic patients and 50 controls completed the evaluations. There were 20 (66.7%) females in the ID group and 29 (58.0%) females in the control group (Table 1). The mean age of ID users was 59.9 ± 13.0 years, which was comparable to the age of controls (53.1 ± 19.2; $P = 0.155$). The IDs of asthmatic patients are described in Table 1. All asthmatic patients received an inhaled corticosteroid. The mean duration of ID use was 130.1 ± 163.2 months. Fourteen (46.7%) asthmatics reported controlled allergies, including dust (5/14), grasses (6/14), pollen (4/14), pet hairs (4/14), trees (4/14), and molds (3/14). The mean alcohol consumption of asthmatics was 0.08 ± 0.25 IU/day. Six asthmatic patients reported a history of tobacco use with a mean of 6.2 ± 1.8 pack-years.

The TREND score was 39.8 ± 19.5 (Table 1), which reports moderate upper aerodigestive and eye mucosa dryness. Laryngopharyngitis symptoms (RSS) and findings (RSA) of ID users and controls are described in Tables 2 and 3. ID users demonstrated significantly higher otolaryngological, digestive, and respiratory scores than controls. The most severe nonspecific symptoms in ID users were excess throat mucus, throat clearing, postnasal drip, and dysphonia (Table 2).

Voice quality evaluations

Videolaryngostroboscopy evaluations reported a significantly higher RSA score in ID users compared to controls. Oral, pharyngeal, and laryngeal subscores and RSA total scores revealed higher values in ID users compared to controls (Table 3). Both judges reported high interrater reliability for RSA assessment (r = 0.951). Emotional, physical, and functional VHI were significantly higher in ID users compared to controls. Similar observations were found for GRBASI evaluations with high interrater reliability between both judges (r = 0.897). The MPT of asthmatics was significantly lower than that of controls. Among acoustic measurements, only STD, percent shimmer, and HNR showed significant differences across groups (Table 4).

TABLE 1.
Demographics

Demographics	ID users (n = 30)	Controls (n = 50)
Mean age (y)	59.9 ± 13.9	53.1 ± 19.2
Gender		
Females	20 (66.7)	29 (58.0)
Males	10 (33.3)	21 (42.0)
Molecules		
Beclomethasone dipropionate	14 (46.7)	-
Budesonide	5 (16.7)	-
Propionate fluticasone	4 (13.3)	-
Fluticasone furoate	5 (16.7)	-
Unspecified IC	2 (6.7)	-
TREND score	39.8 ± 19.5	-

Abbreviations: IC, inhaled corticosteroids; ID, inhaled drugs; TREND, total rating of eye, nasal, and dry-mouth.

Association analyses

Table 5 reports the results of Spearman rank correlation analysis between study parameters. Multiple statistically significant positive correlations were found between subjective and objective voice quality measurements, with correlation coefficients ranging from low to strong. The severity of dysphonia and roughness were strongly correlated with the MPT ($r_s = -0.713$, $r_s = 0.716$). Moderate correlation coefficient was found between percent jitter and breathiness ($r_s = 0.571$).

DISCUSSION

A recent systematic review including 21 studies supported a potential clinical relationship between ID use and the development or perceptual dysphonia, aerodynamic and acoustic parameter impairments.[7] However, the conclusion of the review was limited by the scarcity of controlled studies using multidimensional voice evaluation (eg, subjective, perceptual, aerodynamic and acoustic measurements) for comparing voice quality between ID users and controls. This limitation persists despite guidelines recommending a multidimensional voice quality approach, particularly for correlating perceptual dysphonia with objective findings.[13]

In the present study, multidimensional voice quality evaluations revealed significant subjective and objective impairments in ID users compared to controls. The

TABLE 2.
Symptoms

Reflux Symptom Score	ID users (n = 30)	Controls (n = 50)	*P*-value
Otolaryngological symptoms			
Voice disorder	8.11 ± 8.50	0.57 ± 1.74	< 0.001
Throat pain	2.67 ± 4.42	1.33 ± 4.30	0.003
Odynophagia	2.89 ± 5.99	0.38 ± 1.31	0.036
Dysphagia	4.22 ± 7.63	0.43 ± 1.65	0.003
Throat clearing and postnasal drip	10.30 ± 9.26	1.43 ± 3.44	< 0.001
Globus sensation	8.30 ± 9.19	1.62 ± 3.39	< 0.001
Excess throat mucus	10.40 ± 8.69	2.05 ± 5.07	< 0.001
Ear pressure/pain	5.00 ± 7.63	0.67 ± 1.93	< 0.001
Tongue burning	0.89 ± 3.02	0.14 ± 0.65	0.275
Digestive symptoms			
Heartburn	8.85 ± 8.57	2.38 ± 5.06	< 0.001
Regurgitations or burps	6.70 ± 8.59	1.52 ± 4.71	< 0.001
Abdominal pain	6.22 ± 8.65	1.98 ± 4.94	0.029
Diarrheas	3.56 ± 6.99	0.95 ± 2.27	0.365
Constipation	6.44 ± 9.47	0.90 ± 4.06	< 0.001
Indigestion	2.37 ± 5.36	0.86 ± 2.93	0.338
Abdominal distension/flatus	7.26 ± 9.44	3.69 ± 7.51	0.049
Halitosis	3.59 ± 6.28	1.55 ± 5.37	0.011
Nausea	2.70 ± 6.08	1.86 ± 4.33	0.866
Respiratory symptoms			
Cough after eating/lying down	7.22 ± 7.94	1.48 ± 5.07	< 0.001
Cough	7.67 ± 8.23	0.62 ± 1.82	< 0.001
Breathing difficulties	4.04 ± 6.99	1.21 ± 4.48	0.013
Chest pain	11.7 ± 9.79	1.83 ± 4.57	< 0.001
Reflux Symptom Score	131.30 ± 89.97	29.52 ± 49.46	< 0.001
Otolaryngological score	52.93 ± 39.96	8.93 ± 17.98	< 0.001
Digestive score	47.70 ± 43.87	15.60 ± 25.82	< 0.001
Respiratory score	30.63 ± 23.48	5.00 ± 12.63	< 0.001
RSS - QoL	34.89 ± 21.23	9.50 ± 14.74	< 0.001

Abbreviations: ID, inhaled drugs; QoL, quality of life; RSS, reflux symptom score.

TABLE 3.
Finding Score

Reflux sign assessment outcomes	ID users (n = 30)	Controls (n = 50)	*P*-value
Anterior pillar erythema	3.06 ± 1.72	2.67 ± 2.00	0.658
Uvula erythema ± edema	0.30 ± 0.92	0.01 ± 0.01	0.658
Coated tongue	1.13 ± 1.14	0.63 ± 0.94	0.015
Oral cavity subscore	4.43 ± 2.00	3.11 ± 1.76	0.069
Posterior oro- or hypopharyngeal wall inflammation	0.01 ± 0.01	0.01 ± 0.01	1.00
Tongue tonsil hypertrophy	3.27 ± 2.02	3.00 ± 1.22	0.140
Contact between epiglottitis and tongue tonsils	2.93 ± 1.80	1.78 ± 2.11	0.203
Pharyngeal sticky mucus (dryness)	1.87 ± 2.03	0.89 ± 0.67	0.180
Pharyngeal cavity subscore	8.07 ± 3.61	3.89 ± 3.10	0.005
Ventricular band inflammation	0.53 ± 0.90	0.01 ± 0.01	0.111
Epiglottis inflammation	2.20 ± 1.50	1.33 ± 1.58	0.086
Commissure posterior/arytenoid erythema	2.80 ± 1.86	1.33 ± 2.00	0.050
Interarytenoid granulatory tissue	0.27 ± 0.70	0.06 ± 0.01	0.254
Posterior commissure hypertrophy	2.33 ± 2.54	1.67 ± 2.00	0.247
Retro-cricoid inflammation/edema	2.53 ± 1.96	0.89 ± 1.76	0.032
Endolaryngeal sticky mucus (dryness)	1.50 ± 1.53	0.67 ± 1.32	0.146
Laryngeal subscore	12.40 ± 5.04	5.89 ± 4.04	0.002
Reflux Sign Assessment Total score	24.83 ± 7.30	13.33 ± 6.10	0.001

Abbreviation: ID, inhaled drugs.

TABLE 4.
Voice Quality Outcomes

Voice quality outcomes	ID users (n = 34)	Controls (n = 41)	*P*-value
Patient-reported voice quality			
VHI functional	5.69 ± 7.48	0.33 ± 1.41	< 0.001
VHI emotional	4.54 ± 6.60	0.19 ± 0.89	< 0.001
VHI physical	12.80 ± 9.88	0.36 ± 1.79	< 0.001
VHI total score	23.10 ± 22.70	0.88 ± 4.03	< 0.001
Perceptual voice quality			
Grade of dysphonia	1.25 ± 0.93	0.35 ± 0.52	< 0.001
Roughness	1.07 ± 0.90	0.31 ± 0.51	< 0.001
Breathiness	0.57 ± 0.84	0.02 ± 0.14	< 0.001
Asthenia	0.75 ± 0.84	0.16 ± 0.43	< 0.001
Strain	0.29 ± 0.60	0.06 ± 0.24	0.040
Instability	0.75 ± 0.93	0.14 ± 0.35	0.001
Aerodynamics			
Maximum phonation time	11.10 ± 6.85	14.41 ± 6.25	0.009
Acoustics			
F0 (mean pitch Hz)	180.44 ± 58.27	168.48 ± 50.37	0.476
STD (Hz)	4.78 ± 4.72	2.20 ± 1.52	< 0.001
Jitter (%)	1.03 ± 1.46	0.60 ± 0.40	0.081
Shimmer (%)	8.08 ± 4.63	5.87 ± 2.41	0.022
HNR (dB)	16.77 ± 4.57	20.42 ± 4.33	0.001
SPLmin (dB)	49.92 ± 5.77	49.63 ± 4.95	0.979
SPLmax (dB)	76.78 ± 6.11	75.89 ± 3.94	0.584

Abbreviations: HNR, harmonic-to-noise ratio; ID, inhaled drugs; STD, standard deviation of F0; VHI, Voice Handicap Index.

intergroup difference was particularly pronounced in subjective voice assessments (VHI, GRBASI), which is consistent with previous literature demonstrating that the prevalence of dysphonia is significantly higher when considering VHI/perceptual evaluations (53.3%–89%) than acoustic and aerodynamic impairments/group differences (3%–34%).[7]

Aerodynamic evaluation revealed that MPT was significantly shorter in ID users compared to controls, which partially corroborates the findings of Watkin and Ewanowski who demonstrated a significant reduction of MPT in patients with long-term use of IDs.[17] Aerodynamic and acoustic measurements are interesting objective values when correlated with perceptual voice evaluations. In clinical practice and in the literature, the voice of ID users is commonly described as breathy or hoarse.[18,19] Many authors have reported increased GRB scores in ID users after the initiation of ID therapy.[18–20] In a controlled prospective study, Krishnan et al reported significantly higher GRBAS scores in patients with a 6-month history of ID use compared to new users.[20] Kim et al similarly reported in an observational cohort that GRBAS scores

TABLE 5.
Correlation Analysis

	VHI	Dysphonia	Roughness	Breathiness	TREND	RSS	RSS otol	RSS respi	RSA larynx	RSA
Maximum phonation time	−0.019	−0.713*	−0.716**	−0.429*	−0.332	−0.039	0.053	−0.218	−0.128	−0.032
F0 (mean pitch Hz)	0.039	0.031	−0.015	0.313	0.066	0.313	0.133	0.511**	−0.026	−0.040
STD (Hz)	−0.286	0.427*	0.291*	0.497**	0.034	0.019	−0.159	0.151	−0.070	−0.128
Jitter (%)	−0.124	0.448*	0.175	0.571**	0.174	−0.024	−0.067	−0.141	0.048	−0.096
Shimmer (%)	−0.162	0.301	0.063	0.515**	0.111	−0.134	−0.032	−0.076	0.022	0.013
HNR (dB)	0.077	−0.277	−0.115	−0.353	−0.175	0.137	0.035	0.011	−0.113	−0.172
SPLmin (dB)	−0.154	−0.037	−0.001	0.188	−0.169	−0.263	−0.072	−0.285	−0.185	−0.151
SPLmax(dB)	0.136	0.011	0.023	−0.265	0.107	0.220	0.229	0.052	−0.226	−0.129

*$P < 0.05$.
**$P < 0.01$.
Abbreviations: HNR, harmonic-to-noise ratio; ID, inhaled drugs; RSA, reflux sign assessment; RSS, reflux symptom score; STD, standard deviation of F0; TREND, total rating of eye, nasal, and dry-mouth; VHI, Voice Handicap Index.

significantly increased in the months following the commencement of ID therapy.[18] Despite these similar observations, no study has investigated the association between perceptual and acoustic measurements.[7] In this study, both grades of dysphonia and breathiness were significantly correlated with STD, percent jitter, and percent shimmer, while the reduction of MPT was associated with GRB scores, the severity of mucosal dryness (TREND score), and laryngeal inflammation (RSA). From a pathophysiological standpoint, ID-induced dryness of laryngopharyngeal mucosa, including vocal folds, was reported in a few studies[7,21,22] but poorly investigated prospectively. The dryness of vocal fold epithelium could theoretically alter the vocal fold biomechanical properties and the related vibratory function.[23] The increased STD, percent shimmer, and reduced HNR suggest vibratory impairments in ID users.

To date, very few clinical studies have controlled for confounding factors in ID use clinical cohorts, including active allergy, chronic rhinosinusitis, and laryngitis induced by tobacco and alcohol consumption. Consistent with review recommendations,[7] the authors attempted to control most of these confounding conditions by excluding active/untreated allergies, chronic rhinosinusitis with or without nasal polyps, and tobacco and alcohol-induced laryngopharyngitis. The adherence to carefully defined inclusion and exclusion criteria and the use of multidimensional voice quality evaluations constitute the primary strengths of this study.

The small number of ID patients, the absence of sample size calculation, and the heterogeneity of ID molecules in terms of corticosteroid composition, particle size, and dosages represent the primary limitations of this study. The potential impact of LPRD on voice quality is another potential confounding factor. Given that LPRD is prevalent in both the general population and among otolaryngology outpatients,[24,25] we deliberately included patients with potential LPRD in both study groups rather than excluding them. This balanced distribution approach was designed to neutralize LPRD's effects on voice quality measurements through statistical equilibration. Future studies investigating voice quality alterations in ID users without confounding variables should consider implementing 24-hour HEMII-pH testing to definitively exclude LPRD patients, as both RSS and RSA include nonspecific symptoms and findings commonly observed in both LPRD- and ID-induced laryngopharyngitis.

CONCLUSION

ID users demonstrated impaired multidimensional subjective and objective voice quality evaluations compared to controls. Future controlled mechanistic studies are needed to better understand to relationship between ID and vocal fold function impairments.

Institutional review board statement

The local IRB approved the study.

Informed consent statement

Patients and controls consented to participate.

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Author contributions

Jerome R. Lechien: Design, acquisition of data, data analysis & interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **Isra Slimani**: Design, acquisition of data, data analysis & interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability

Not applicable.

Declaration of Competing Interest

The authors declare no conflict of interest.

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