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Patient sensitization profile and fish species' tolerance in children with IgE-mediated fish allergy

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Abstract

Background: Fish allergy remains a poorly investigated topic despite its potential severity and impact on child well-being. There is a paucity of data on IgE fish allergy in pediatric patients in the Mediterranean region.

Methods: 52 children with IgE-mediated fish allergy underwent OFCs with different fish species. The adopted OFC protocols were according to PRACTALL Consensus. Nonparametric quantitative variables were compared between two groups using the Mann-Whitney U test, and the data were visualised using box plots. Fisher's exact test was used to assess the significance between dichotomous categorical variables.

Results: A total of 72 OFCs were performed over time; 17/52 patients underwent an OFC for at least two different fish species. 52/58 patients (89.6%) successfully overcame OFCs with fish species other than the trigger one, mostly tuna (19/21; 90.5%), salmon (15/17; 88.2%), and swordfish (6/6 100%), respectively. slgE for tested fish were positive in 41 out of negative OFCs (41/62; 66.1%) and in 5 out of 10 positive OFCs (5/10; 50%), respectively. Fish-slgE levels were >10 kUA/L (range 12.3-37.5 KU/Lt). slgE levels between positive and negative OFCs were not significantly different (Mann-Whitney U test, P = 0.33). Moreover, no significant association between slgE levels and the OFC outcome (Fisher's exact test, P = 0.18) was observed.

Conclusions: Patients with IgE-mediated fish allergies can safely consume one or more fish species, especially tuna, salmon, and swordfish. Tolerance should be confirmed by an OFC, since the slgE levels do not predict clinical reactivity.

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Key Message

Patients with IgE-mediated fish allergies can safely consume one or more fish species, especially tuna, salmon, and swordfish. Tolerance should be confirmed by an OFC, since sIgE levels do not predict clinical reactivity.

Introduction

Fish allergy remains a poorly investigated topic despite its potential severity and impact on child well-being. Fish serves as a source of high-biological-value proteins, omega-3 fatty acids in the form of docosahexaenoic acid (DHA), which is crucial for the development of neural structures, and calcium and fluorine.¹ Due to its nutritional properties, potential nutritional deficiencies may occur in the case of a prolonged avoidance diet.

Epidemiological data on fish allergy prevalence in European children are limited and mostly based on parental-reported questionnaires.²⁻⁸ Considering oral food challenge (OFC)-based data, the only up-to-date available evidence comes from Nwaru et al.'s meta-analysis, with an estimated point prevalence of fish allergy of 0.6%,⁹ and also according to epidemiologic data from the Europrevall study.¹⁰ However, epidemiological data vary according to each region, and in Europe, fish allergy is particularly widespread especially in coastal regions such as Scandinavian and Mediterranean areas, likely due to the high consumption of fish in the diet.⁹

The most common type of hypersensitivity reactions to fish is Immunoglobulin E (IgE)-mediated fish allergy, which can be responsible for severe allergic reactions in young children⁶⁻⁸ and can persist into adulthood.⁶⁻⁸

In clinical practice, it is widely acknowledged that patients who experience an IgE-mediated allergic reaction to a specific fish may exhibit reactions to other fish species.^{6-8,11} The cross-reactivity among fish species is mainly due to specific IgE (sIgE) for beta-parvalbumin (β -PV), which is the major allergen present in all bony fish,^{6-8,11} responsible for clinical manifestations in 90% of fish allergic patients.^{6-8,11} The β -PV of different fish species shows a high sequence identity (55-95%) and is considered as a fish panallergen.¹¹

Allergy to one or more fish species in patients with sIgE for β -PV is not only related to the structural similarity of β -PVs chains among fish species, but it also depends on its concentration in the muscle of the various fish species.¹² In fact, the β -PV has its highest concentration in the white muscle of bony fish, while the red muscle contains very low levels of it. Since the proportion of white and red muscle varies between species, the β -PV content also varies.¹³

Other fish allergens have been recognized as responsible for cross-reactivity among different fish species. Among these, enolase and aldolase, identified as major heat-labile fish allergens, can cause an allergy to cod and salmon in patients not sensitised to β -PV, and to tuna and swordfish, which have a lower β -PV content than other fish.¹⁴

Since cross-reactivity among different fish species exists,¹⁵ it is a common practice to recommend an avoidance diet for all fish species in patients with fish allergies, especially in cases of positivity for sIgE to other fish in addition to the trigger one.

However, this recommendation may be too strict in many cases, as studies on both paediatric and adult patients with fish allergies have shown that serological cross-reactivity does not imply clinical cross-reactivity.¹⁶⁻¹⁸

Furthermore, studies in paediatric patients have shown that at least some of them can tolerate one or more species other than the trigger fish.^{19,20} A Chinese research group conducted a study of 249 fish-allergic children, making it the largest paediatric study on fish allergy to date. Among all the patients, only 30% reacted to one or more fish species in OFCs, and the majority of the population was selectively tolerant of certain fish species.¹⁹ In Europe, a Greek study showed that most children with a confirmed diagnosis of IgE-mediated fish allergy could consume at least swordfish and tuna.²⁰

Surprisingly, despite fish holding particular significance within the context of the Mediterranean diet, there is a paucity of data on fish allergy in pediatric patients.

This is particularly relevant given the well-documented benefits of the Mediterranean diet on children's health and its protective effect against various chronic diseases, most notably in the prevention and management of asthma.²¹

We therefore aimed to investigate the clinical significance of sensitization to different fish species in children with a diagnosis of fish allergy.

Methods

Study population

The study population consisted of 52 children with a suspected IgE-mediated fish allergy, consecutively admitted to two paediatric Allergy Units in northern Italy, Buzzi Children's Hospital (Milan) and Regina Margherita's Hospital (Turin) from January 2017 to February 2024.

Informed consent was obtained from the parents of patients involved. The study was approved by the Ethical Committee (protocol number 22050).

A complete diagnostic work-up was performed, including sIgE to a panel of different fish species by Immuno-Cap system (Thermo Fisher Scientific, Uppsala, Sweden), with a cut-off positive point > 0.10 KU/l. Skin prick tests (SPT) were considered positive if the wheal diameter was greater than 3 mm.

All patients were on a fish-free diet at the time of admission, and none reported severe reactions in the 12 months prior to admission. All patients underwent OFCs in a hospital setting with an available intensive care unit. Most of the patients underwent an OFC with fishes different from the culprit one (if reported in the clinical history; if the culprit fish was unknown, the fish species to be tested by an OFC was chosen by the paediatric allergist on the basis of clinical history, patient sIgE profile and also on family habits and preferences). Some patients also underwent an OFC to evaluate tolerance to the culprit fish.

Most of the OFCs were conducted as open or single-blind challenges as per clinical practice. The adopted OFC protocols in both centres relied on PRACTALL Consensus.²²

The target cumulative dose was defined in order to reach an age-appropriate portion of fish.

OFCs were performed under medical supervision by expert pediatric allergologists, at Tertiary level Hospital, and with the support of a skilled dietitian.

Challenges were considered positive if objective symptoms of an IgE-mediated reaction occurred. Immediate allergic manifestations to OFCs were classified into the following categories: muco-cutaneous reactions (erythema, urticaria, angioedema), gastrointestinal symptoms (vomiting, abdominal cramps, diarrhea, oropharyngeal pruritus), respiratory symptoms (laryngeal edema, wheezing, coughing, hoarseness, dyspnea, chest tightness), ocular symptoms, nasal symptoms, cardiovascular symptoms (hypotension, loss of consciousness, shock), and anaphylaxis. They were also ranked according to the grading system for acute allergic reactions developed by Sampson et al so as to score the final severity grade (mild, moderate, or severe) of adverse reactions during OFCs,²² and the subgrading system, which can be used to determine the severity (mild, moderate, or severe) of symptoms specific to each organ involvement.²³ For positive OFCs, the appropriate treatment was given

depending on the type and severity of the allergic manifestation. In the event of a negative OFC, before discharge, indications were provided by the dietitian for the reintroduction of the food at home (Figure 1).

Data analysis

Descriptive analysis was used in order to evaluate patient features and OFC outcomes. Qualitative variables were presented as %, and for quantitative variables, the mean with standard deviation and the median were calculated.

Data was also analysed using R software. The Shapiro-Wilk test was performed to test the normality of the data. Nonparametric quantitative variables were compared between two groups using the Mann-Whitney U test, and the data were visualised using box plots. Fisher's exact test was used to assess the significance between dichotomous categorical variables. In all analyses, statistical significance was indicated by p-values < 0.05.

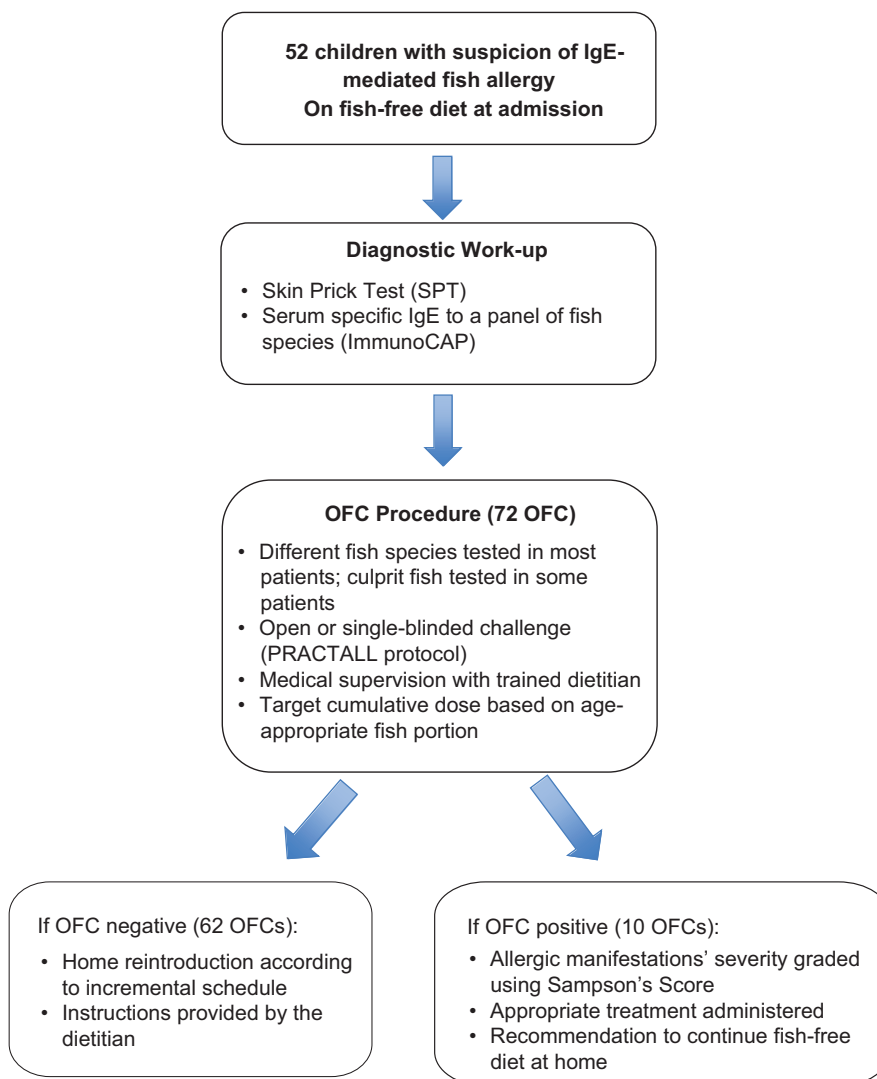


Figure 1 Diagnostic and management flowchart for patients evaluated for fish allergy.

Results

Study population characteristics

A total of 52 children were included in the study. Demographic and clinical features are reported in [Table 1](#). The mean age of symptoms onset was about 2 years and 11 months (2 y 11 m). Forty-seven out of fifty-two patients reported the culprit fish (for some children more than one) to be: 17/52 (32.7%) cod, 12 (23%) flounder, 8 (15.4%) salmon, 7 (13.5%) bream, 7 (13.5%) hake, 6 (11.5%) sole, 4 (7.7%), trout, 4 (7.7%) european bass, 3 (5.8%) tuna, 3 (5.8%) swordfish, 2 (3.8%) mackerel, 2 (3.8%) perch, and 3 (5.8%) other fish species.

The most common presenting symptom was urticaria, followed by other mucocutaneous symptoms. Many patients also experienced gastrointestinal symptoms within 2 hours of ingestion. 19/52 children (36.5%) reported a clinical history of anaphylaxis.

Five patients (9.6%) presented with symptoms of skin contact ($n = 2$, cutaneous erythema after direct contact and $n = 1$, kiss-induced allergy), inhalation of cooking vapours ($n = 1$, conjunctival hyperaemia and facial erythema), and contamination of the fork with fish ($n=1$, erythematous rash and itching).

Oral food challenges

A total of 72 OFCs were performed over time; 17/52 patients underwent OFC for at least two different fish species, 58/72 OFCs were performed with fish species other than the trigger one, and 14 OFCs were performed to evaluate tolerance to the culprit fish.

Table 1 Baseline characteristics of study population.

	N (%)
Male	31 (60)
Female	21 (40)
Family history of allergy	28 (54)
Overall Atopy	45 (86.5)
Atopic Dermatitis	32 (61.5)
Allergic rhinoconjunctivitis	15 (29)
Allergic asthma	8 (15.5)
Other food allergy	29 (56)
First reaction to fish	
Urticaria	30 (58)
Symptoms with skin contact	5 (9.6)
Angioedema	15 (29)
AD worsening	2 (4)
Gastrointestinal symptoms	25 (48)
Vomiting	20 (38.5)
Diarrhoea	2 (4)
Oropharyngeal pruritus	5 (9.5)
Wheezing	12 (23)
Anaphylaxis	19 (36)
Average age at first reaction	2 years and 11 months

The mean age at the OFC was 9 y 6 m \pm 4 y 7 m (range 8 months-17 years 10 months; median and interquartile range 10 \pm 7.5 years). Fifty-two out of 58 patients (89.6%), undergoing an OFC with fish species other than the trigger one, successfully overcame OFCs: 19/21 (90.5%) for tuna, 15/17 (88.2%) for salmon, 9/11 (82%) for codfish, 6/6 (100%) for swordfish, 2/2 (100%) for flounder, and 1/1 (100%) sole, respectively.

Fourteen children underwent an OFC with the culprit fish; 10/14 (71.4%) successfully passed the OFC: 3/3 (100%) for tuna, 1/2 (50%) for salmon, 3/4 (75%) for codfish, 0/2 for swordfish, 1/1 (100%) for sole, mackerel, and hake, respectively.

Six out of 10 positive OFCs were performed as open challenges, 3 as single-blind challenges, and 1 as a double-blind challenge.

Allergic reactions during OFCs included mucocutaneous symptoms (6/10 patients experienced only urticaria) and gastrointestinal symptoms (vomiting in only 4/10). Considering the severity of reactions in all positive OFCs, the mean Sampson Score [+] was 1.3 (70% grade I, 30% grade II). No cases of anaphylaxis occurred. In 3/10 positive OFCs, the child reacted after administration of the last dose.

Of the 26 OFCs performed in children with a clinical history of past anaphylaxis ($n= 19$), 4 (15.4%) were positive, while the majority of patients 16/19 (84.2%) successfully completed the OFC with at least an alternative fish species.

Fish sensitization and OFC outcome

Specific IgE levels for the tested fish were available for all patients, as were panels of at least 3 sIgE for other fish species (see [Table 2](#)).

Specific IgE for the tested fish was positive in 41 out of 62 negative OFCs (41/62; 66.1%) and in 5 out of 10 positive OFCs (5/10; 50%), respectively. Fish-sIgE levels were >10 kUA/L (range 12.3-37.5 kUA/L) in 6/62 (9.7%) of negative OFCs and in 1/10 (10%) of positive OFCs.

Comparing sIgE levels between the two groups, the mean value was comparable (3.2 for negative OFCs and 1.6 for positive OFCs). The standard deviation calculated in both groups resulted in the same value (8 kU/L). The median value and interquartile range were 0.1 \pm 1.3 and 0.1 \pm 1.9 in negative and positive groups, respectively.

The Shapiro-Wilk test performed on the sIgE levels revealed that the data were not normally distributed ($P < 0.0001$).

The comparison of sIgE levels between positive and negative OFCs did not reveal a statistically significant difference (Mann-Whitney U test, $P = 0.33$). Moreover, no significant association between sIgE levels and the outcome of the OFC (Fisher's exact test, $P = 0.18$) was detected in our population (see [Figure 2](#)).

Skin Prick Test data were recorded for 45 patients, but they were sometimes inconsistent with serological results (6 patients showed negative SPT but positive sIgE for tested fish).

Of the entire study population, follow-up data was obtained in 33/52 subjects.

After a negative OFC, most children reintroduced fish into their diet (tested fish and/or other fish), without

Table 2 sIgE and OFCs outcome.

	Negative OFCs (n 62)	Positive OFCs (n 10)	Total OFCs (n 72)
Mean value sIgE \pm SD	3.2 \pm 8 kU/L	1.6 \pm 8 kU/L	3 \pm 7.5 kU/L
Positive sIgE	41/62 (66.1%)	5/10 (50%)	46/72 (63.9%)
0.10-1 kU/L	10/62 (16.1%)	1/10 (10%)	11/72 (15.2%)
1-10 kU/L	25/62 (40.3%)	3/10 (30%)	28/72 (38.9%)
>10 kU/L	6/62 (9.7%)	1/10 (10%)	7/72 (9.7%)
Negative sIgE	21/62 (33.9%)	5/10 (50%)	26/72 (36.1%)
Mean age at OFC \pm SD	9 y 5 m \pm 4 y 6 m	10 y 5 m \pm 5 y 1 m	9 y 6 m \pm 4 y 7 m
Tested fish			
Salmon	16/62 (25.8%)	3/10 (30%)	19/72 (26.4%)
Tuna	22/62 (35.5%)	2/10 (20%)	24/72 (33.3%)
Codfish	12/62 (19.3%)	3/10 (30%)	15/72 (20.8%)
Swordfish	6/62 (9.7%)	2/10 (20%)	8/72 (11%)
Other fish species	6/62 (9.7%)	0	6/72 (8.3%)

Abbreviations: OFC (oral food challenge), SD (standard deviation), sIgE (specific Immunoglobulin E), y (years), m (months).

adverse reactions (27/33, 82%). However, two patients refused to eat fish due to taste issues or for fear of severe reactions. Others (3/33, 9%) experienced mild allergic manifestations after trying fish at home, despite the positive outcome of the OFC (oral allergy syndrome in two cases after the consumption of salmon, and pharyngeal itching and mild labial edema after consuming tuna in one case).

Discussion

This study analyzed a cohort of 52 children with IgE-mediated fish allergy and found that the majority (89.6%) tolerated at least one fish species other than the culprit, including patients with a history of past anaphylaxis. Specific IgE levels did not significantly correlate with OFC outcomes.

Fish is considered one of the main food triggers for IgE-mediated allergy in childhood, sometimes causing anaphylactic reactions.^{6,8} In clinical practice, children with IgE-mediated fish allergy are generally recommended to avoid all types of fish, based on the fear of clinical cross-reactivity.

In our study, most children who underwent OFCs with a fish other than the culprit fish were able to tolerate one or more different fish species.

In particular, tuna and swordfish were tolerated by 91.6% and 75% of our patients, respectively, in agreement with the percentages reported by Xepapadaki et al in 58 children with IgE-mediated fish allergy.²⁰ The explanation for these findings is likely that tuna and swordfish are β -PV-poor fishes (< 0.05 mg of β -PV/g of fresh fillet);¹¹ hence, these fish species can be tolerated by patients who are sensitized and reactive to this protein.

Flounder and sole have a low β -PV content (0.3 mg/g),¹¹ too, and it is possible to hypothesize that they were tolerated by the patients to whom they were offered as an alternative to hake and cod, acting as trigger fish.

Notably, salmon was tolerated by the majority of our patients (84.2%). In a large Chinese study conducted on 249 fish-allergic children, Leung et al.¹⁹ reported that the most

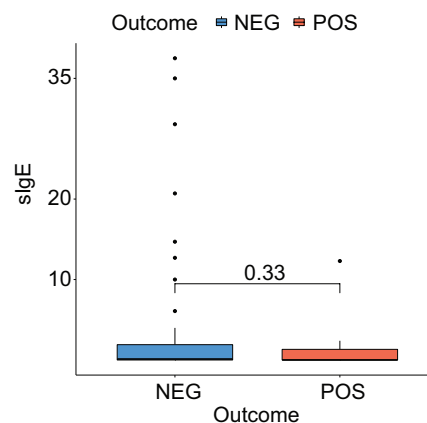


Figure 2 Boxplot comparison of specific IgE levels between patients with positive and negative OFCs. No statistically significant difference was observed between the two groups (Mann-Whitney U test, $P = 0.33$).

common fish species to which the participants demonstrated tolerance was salmon (28.5%).

Salmon has a species-specific IgE epitope of β -PV and the cross-reactivity with the β -PV of other bony fishes is absent.^{11,24}

Our patients tolerated salmon at a higher percentage than those observed in the Chinese study by Leung et al. This result is noteworthy, since salmon is particularly rich in omega-3 long-chain polyunsaturated fatty acids; thus, its reintroduction into the diet may help reach the recommended omega-3 dietary intake.²⁵

Our findings seem to differ from epidemiological data, which have described fish allergies as life-long in most cases.^{26,27} More recently, however, it has been shown that about half of fish-allergic children may develop tolerance in adolescence,²⁰ in agreement with data from another retrospective study showing that up to 63% of patients may overcome fish allergy at an average age of 10.5 \pm 10.2 years.²⁸ Such observations, along with ours, highlight the importance

of periodically reassessing fish tolerance acquisition so as to avoid unnecessary prolongation of an elimination diet.

Regarding systemic reactions due to fish allergy, we found that 84% of our patients with anaphylaxis at onset, successfully passed an OFC with one or more fish species. Patients with positive OFCs exhibited solely mild reactions, including muco-cutaneous and gastrointestinal symptoms. No episode of anaphylaxis occurred, although four of them experienced an anaphylactic reaction at onset. No children required hospitalisation, which is consistent with findings from previous studies.^{18,28}

Our data suggest that the severity of the first reaction does not correlate with the OFC outcome.

In our study, sIgE levels between OFCs with positive outcomes and those with negative outcomes were not significantly different. In 50% of positive OFC cases, sIgE was negative, despite clinical reactions to OFC being distinctly IgE-mediated; on the other hand, among the negative OFC group, 6/62 (9.7%) patients had sIgE >10 kUA/L, four of which had sIgE >20 kUA/L. In recent years, several authors have tried to identify a specific cut-off point for sIgE levels to predict fish OFC with a positive predictive value,^{18,29-32} but considerable variability renders them useless in clinical practice. Recent Guidelines suggested using sIgE levels with caution and adapting them to clinical characteristics of patients.²²

In our study, the mean age of first reaction to fish was about 2 years and 11 months. Forty-four out of fifty-two patients experienced allergy onset between 6 and 24 months. This result was in line with the existing literature, which reported a peak in fish allergy incidence in the first 2 years of life.⁶⁻⁸

In our study cohort, most children had a high prevalence of atopy (86.5%), and in particular 61.5% of patients were affected by atopic dermatitis (AD), in agreement with what has been observed by other authors.^{28,33} The results of SPT were not taken into account due to the high prevalence of AD in tested children and to their recognized poor reliability in fish allergy, given that allergenicity of fish extracts may be altered by the preparation process.³² Similar to what was reported by Kuhnen et al.,¹⁴ no correlation was found between the degree of skin reactivity (wheal diameter) and the specific serum IgE levels.

Our study has some limitations. First, the retrospective design; second, most patients underwent OFCs with one or two fish species; third, most challenges were open or single-blind, while only a few parts of the OFCs were conducted in double-blind mode.

Conclusions

This study adds to the knowledge on fish allergy in children from a Mediterranean country, which is characterized by a fish-rich diet. We were able to demonstrate that patients with IgE-mediated fish allergies can safely consume one or more fish species and that sIgE levels to one or more fish species do not predict clinical reactivity. In clinical practice, this translates into a need to perform OFCs, as fish is rich in nutrients and should not be excluded from children's diets unless necessary.

Whenever an alternative fish is proposed to the one that caused the reaction, the first species to be reintroduced

should be those with the highest probability of tolerance, such as tuna, salmon, and swordfish, which must be confirmed by an OFC.

Finally, our findings highlight the importance of periodically re-evaluating the effort to overcome fish allergies in order to avoid the unnecessary prolongation of an elimination diet.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this article.

Conflict of Interest

All authors report no conflict of interest for this manuscript.

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