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Original Article

The Utility of Contrast-Enhanced 3D-Real Inversion Recovery Magnetic Resonance Imaging in the Diagnosis of Endolymphatic Hydrops—A Retrospective Study of a Newly Implemented Clinical Service at a Tertiary Center

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BACKGROUND: Over the last decade, delayed gadolinium-enhanced magnetic resonance imaging (MRI) of the inner ear has become increasingly used as an objective marker for the diagnosis of endolymphatic hydrops (EH) in Ménière's disease (MD). This study evaluates the utility of this imaging technique in the first 100 patients scanned at our tertiary center.

METHODS: A retrospective study was conducted in the Department of Otology and Neuro-otology at University College London Hospitals between October 2020 and May 2022. Patients were classified into 4 groups: "definite MD," "probable MD," isolated cochlear symptoms, and MD-vestibular migraine (VM) overlap syndrome. The local imaging protocol consisted of an intravenous gadolinium (IV-Gd) injection followed by T2 SPACE and 3D-real inversion recovery magnetic resonance imaging (MRI) of the inner ears after 4 hours.

RESULTS: The first 100 patients scanned were included. All patients with "definite MD" and MD-VM overlap syndrome had evidence of radiological EH on MRI. About 38% of patients in the "probable MD" group and 25% of patients in the isolated cochlear hydrops group had radiological EH. For the "definite MD" group, 98% of positive scans correlated with disease laterality; this was 87% in the "probable MD" group. Duration of disease >4 years and more severe hearing loss were found to be statistically significant factors for the detection of EH.

CONCLUSION: Our study demonstrates that EH is much more likely to be detected in patients with a clinical diagnosis of "definite MD" or MD-VM overlap syndrome, and also correlates with the increasing duration and severity of symptoms. Further studies using standardized imaging protocols would be helpful in comparing outcomes.

KEYWORDS: Meniere's disease, otoneurology, vestibular diseases, vestibular migraine

INTRODUCTION

Endolymphatic hydrops (EH) is an inner ear disorder characterized by the expansion of the endolymphatic space into the adjacent perilymphatic space. The etiology is not fully understood but is widely attributed to the disruption of endolymph ion transport and regulation.[1] It is classified as primary (idiopathic) or secondary EH, and may be symptomatic or asymptomatic. The term Ménière's disease (MD) is used to describe a clinical disorder characterized by symptoms that include spontaneous episodes of vertigo, low- to mid-frequency hearing loss, and fluctuating aural symptoms, such as tinnitus and aural fullness.[2,3]

In 1995, the "Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery" (AAO-HNS) published a guideline to aid with the diagnosis of MD.[4] This classification established 4 disease categories: certain, definite,

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probable, and possible MD. Certain MD was a post-mortem diagnosis following histopathological examination in those who fit the criteria for definite MD.[4] In 2015, the "Classification Committee of the Bárány Society" (CCBS) published simplified diagnostic criteria for MD, with just 2 categories: definite MD and probable MD.[5] This more recent guideline has come under criticism for its emphasis on symptoms rather than objective measures such as clinical examination findings and diagnostic testing.[6] Despite these classification systems, the diagnosis of MD remains challenging because of the variability of symptom onset and duration, in addition to the overlap of symptoms with other conditions such as, but not limited to, vestibular migraine (VM).[5,6,7,8] Whereas previously the purpose of imaging in MD was to exclude alternative pathologies, gadolinium-enhanced delayed inner ear magnetic resonance imaging (MRI) can now directly demonstrate EH.[7,9,10,11]Both intratympanic gadolinium- (IT-Gd) and intravenous gadolinium (IV-Gd)-enhanced MRI have shown accumulation of contrast within the perilymph, outlining the unenhanced endolymphatic space. Over the past 10 years, IV-Gd has gained popularity as it is more convenient and allows assessment of both ears at the same time.[12-13,14,15] The benefit of confirming EH using these MRI techniques includes distinguishing MD from its differential diagnoses and assessing for bilateral disease, both of which are helpful in cases where invasive treatment is being considered. Imaging may in the future play a role in providing prognostic information.[10]

The aim of this study was to evaluate the utility of IV-Gd-enhanced 3D-Real inversion recovery (IR) MRI in the diagnosis of EH for the first 100 patients scanned at our institution.

METHODS

Patient Selection

This retrospective study was conducted in the Department of Otology and Neuro-otology at Univesity College London Hospitals NHS Foundation Trust. Data used in this study were retrieved from patient electronic medical records (EPIC Systems Corporation, USA) between October 2020 and May 2022. Local criteria for referral for EH MRI protocol accord with the wider literature, including VM overlap, diagnostic uncertainty, bilateral MD symptoms, fluctuating aural symptoms as the only presenting symptom, and those planned for ablative labyrinthine surgery. Patients were classified into 4 groups: clinically "definite MD," clinically "probable MD," isolated cochlear symptoms, and MD-VM overlap syndrome. The isolated cochlear symptoms group included patients who had fluctuating aural symptoms, including hearing loss, tinnitus, and ear fullness with audiometrically evident low- to mid-frequency sensorineural hearing loss. The MD-VM overlap group included "definite MD" patients who simultaneously met the Bárány Society criteria for "definite VM."[16,17] Patients were recorded as having either unilateral or bilateral symptoms and were scanned within 3 months of an active episode of symptoms.

Imaging Techniques and Analysis

All studies were performed using the MRI protocol described by Bernaerts et al,[15] which consists of an IV-Gd injection followed by a 3D-real IR MRI of the inner ears after 4 hours. Images were assessed for EH using the system proposed by Baráth et al[18] as adapted by Bernaerts et al,[15] (Table 1), by consultant radiologists with 5-25 years of experience in head and neck imaging. A scan was considered positive if any grade of cochlear and/or vestibular endolymphatic hydrops was detected.

Figure 1 shows examples of 3D-Real IR EH protocol imaging from our institution.

Pure Tone Audiometry

Pure tone audiometry (PTA) average thresholds at 500, 1000, 2000, and 4000 Hz were calculated and stratified as mild, moderate, severe, or profound hearing loss, in line with the British Society of Audiology Classification.[19]

Statistical Methods

The data were analyzed with SPSS 26.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA). Somers' *d* test, independent-samples Mann–Whitney *U*-test, and one-way analysis of covariance (ANCOVA) were used for data analysis. A *P*-value was considered to be statistically significant if less than .05.

MAIN POINTS

- Gadolinium-enhanced magnetic resonance imaging (MRI) of the inner ears is highly sensitive and specific for detecting endolymphatic hydrops (EH) in patients clinically diagnosed with definite Ménière's disease (MD) and MD with vestibular migraine (MD-VM) overlap syndrome. The sensitivity is much lower for probable MD, but the specificity remains high.
- The positivity rate and severity of EH on contrast-enhanced 3D-Real inversion recovery (IR) MRI correlated with the increasing duration and severity of symptoms.
- Radiological EH correlated with the symptomatic side(s) in 98% of patients in the "definite MD" group, 87% of patients in the "probable MD" group, and 66% of patients in the "isolated cochlear symptoms" group.
- The grade of vestibular endolymphatic hydrops might be higher in MD-VM overlap syndrome compared to MD.
- Gadolinium-enhanced MRI of the inner ears may be particularly useful for patients being considered for interventions such as intratympanic steroids or surgery, and may be used to provide prognostic information in the future.

Table 1. Grading System for Endolymphatic Hydrops on MRI IAM with IV-Gd

Cochlear Hydrops—Grading Determined by Displacement of Reissner's Membrane (RM)	
0	None; no displacement of RM
1	Mild hydrops; displacement of RM but endolymphatic space < scala vestibuli area
2	Significant hydrops; displacement of RM and endolymphatic space > scala vestibuli area
Vestibular Hydrops	
0	Saccule and utricle are separate and <50% of vestibular surface
1	Saccule ≥ utricle but not confluentt
2	Saccule and utricle are confluent with a peripheral rim of perilymph enhancement
3	Bony vestibule is fully obliterated

RM, Reissner's membrane.

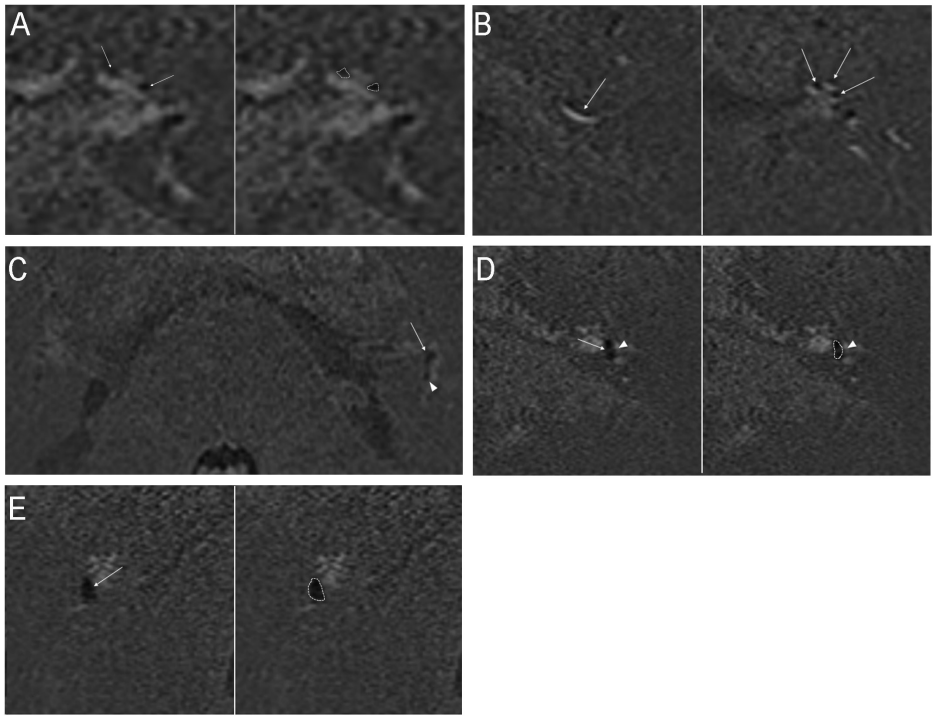

Figure 1. Axial delayed IV-Gd-enhanced 3D-Real IR EH hydrops protocol images from our institution. (A) Cochlear hydrops grade I: the scala media is indirectly visible as a "nodular black cut-out of the scala vestibuli" (arrows and dashed outlines). (B) Cochlear hydrops grade II: the image on the left shows the cochlea at the level of the lower basal turn and shows a distended scala media (arrows) that completely obliterates the scala vestibuli. The image on the right shows the same cochlea at the mid modiolar level, again showing a fully obliterated scala vestibuli at all levels (arrows). (C) Vestibular hydrops grade I: the left saccule (arrow) is equal to or larger than the utricle (arrowhead). (D) Vestibular hydrops grade II: the left saccule and utricle (arrow and dashed lines) are confluent with a residual peripheral rim of perilymph enhancement (arrowhead). (E) Vestibular hydrops grade III: complete obliteration of the bony vestibule (arrow and dashed lines).

RESULTS

One hundred patients satisfied the inclusion criteria within the study period (October 2020-May 2022). The age range was 15-78 years with a mean age of 49 years. Of these, 49 patients were diagnosed with clinically "definite MD" and 39 with "probable MD" according to the 2015 CCBS MD diagnostic criteria.[4] The former included 25 patients with MD-VM overlap syndrome. Twelve patients had isolated cochlear symptoms (Figure 2). Sixty-four patients presented with unilateral and 24 patients with bilateral MD symptoms.

Correlation Between Clinical Symptoms and Findings at MRI

Endolymphatic hydrops was demonstrated on imaging in 67 of the 100 patients (67% of the study population). Of the 49 patients with clinically "definite MD," EH was shown on MRI in all 49 patients (100%) and correlated with the symptomatic side(s) in 48 of the 49 patients (98%). One patient had bilateral symptoms but was found to have unilateral EH on MRI. Of the 39 patients with clinically "probable MD," EH was shown on MRI in 15 patients (38%) and correlated with the symptomatic side(s) in 13 of the 15 patients (87%). Of the 12 patients with isolated cochlear symptoms, EH was shown on MRI in 3 patients (25%) and correlated with the symptomatic side(s) in 2 of the 3 patients (66%) (Figure 2).

Twenty-five patients (25%) were clinically diagnosed with MD-VM overlap syndrome, all of whom were shown to have EH on MRI.

An ANCOVA test was used to compare the grade of cochlear EH (cEH) and vestibular EH (vEH) in the MD group (including both definite and probable) with the MD-VM overlap group after controlling for average PTA and duration of symptoms. It found a statistically significant difference in the grade of vEH between the 2 groups, $F(1, 97) = 3.94$, $P < .05$, partial $\eta^2 = 0.039$. Post hoc analysis was performed with a Bonferroni adjustment. The grade of vEH was significantly higher in the MD-VM overlap group compared to the MD group (mean difference 0.786 (95% CI, 0.140-1.432), $P < .05$). There was, however, no significant difference in the grade of cEH between the MD group and the MD-VM overlap group, $F(1, 97) = 1.140$, $P = .288$, partial $\eta^2 = 0.012$.

Correlation with Symptom Duration

Duration of symptoms was grouped into greater than 4 years versus less than or equal to 4 years, as described in an earlier study by Fujita et al.[20] Endolymphatic hydrops was evident on MRI in 50.9% of patients with symptom duration of 4 years or less, and 87.5% of patients with symptoms for more than 4 years. A Somers' *d* test demonstrated a statistically significant positive correlation between the duration of symptoms and both cEH and vEH on MRI ($d = 0.207$ for cochlear EH and 0.209 for vestibular EH; $P < .005$) (Figure 3A and B).

Correlation with Hearing Thresholds

A statistically significant positive correlation between the severity of hearing loss (average PTA) and the presence of cochlear and vestibular EH on MRI was also found using Somers' *d* test ($d = 0.383$ for cochlear EH and 0.357 for vestibular EH; $P < .0005$) (Figure 3C and D). Audiograms could not be retrieved for 5 patients.

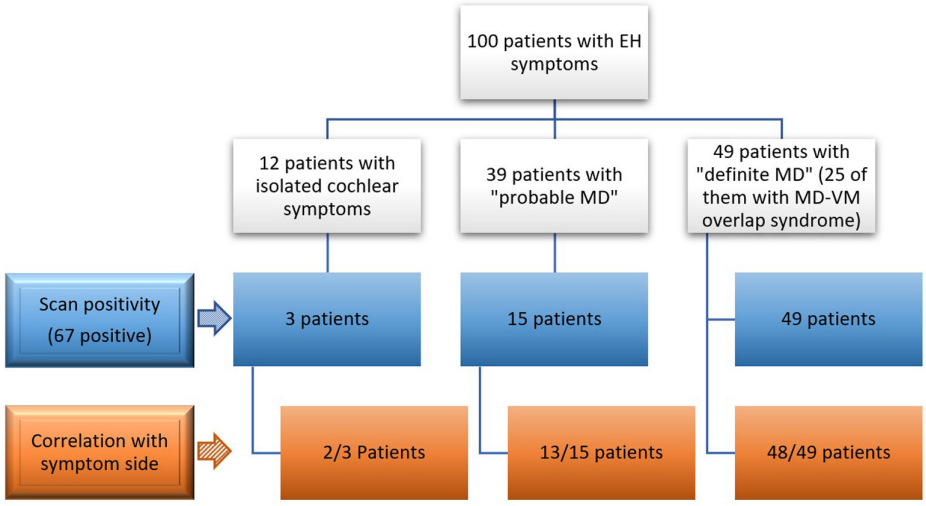

Figure 2. Breakdown of study sample, positivity of endolymphatic hydrops on delayed contrast-enhanced MRI of the inner ears, and correlation with symptom laterality. Key: EH, endolymphatic hydrops; MD, Ménière's disease; MD-VM overlap syndrome, Ménière's disease with vestibular migraine overlap syndrome.

DISCUSSION

Ménières Disease

Over the past decade or so, delayed IV-Gd-enhanced MRI has been increasingly used to evaluate patients with Ménièriform symptoms, in the hope of developing a gold-standard diagnostic test that can objectively confirm the diagnosis of EH *in vivo*, particularly in patients in whom intervention is being considered, and to clarify the diagnosis in patients with symptoms that are variable, atypical, and/or overlap with other clinical diagnoses. The detection rate of EH on MRI is widely variable in the literature.[21] However, a recent meta-analysis found that "increased perilymphatic enhancement, alone or in combination with any EH" demonstrated the highest diagnostic odds ratio and achieved optimal sensitivity (87%) and specificity (91%) for MD.[22] This is comparable to histopathologic data, which demonstrated the presence of EH in 93% of patients who had a clinical diagnosis of MD.[23] In our study, assessment of the imaging was limited to cochlear and vestibular hydrops; nevertheless, we have demonstrated that IV-Gd-enhanced 3D-real IR MRI corroborates previous findings that this technique is highly sensitive (100%) and specific (97.44%) for definite MD. Whereas for probable MD, the sensitivity was only 30.77%, although specificity remained high at 95%. It must be noted, however, that bilateral MD can be present in 5-50% of patients, and therefore patients with unilateral radiological EH may

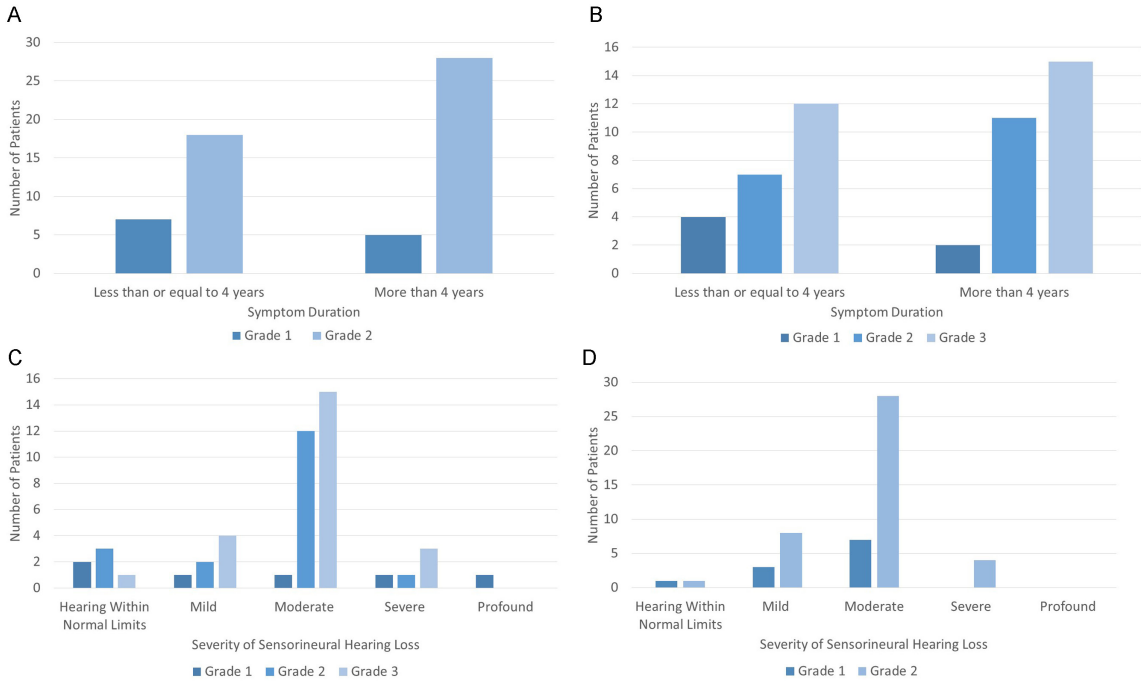

Figure 3. Correlation between duration of symptoms, degree of hearing loss, and radiological endolymphatic hydrops (EH). (A) Duration of symptoms and grade of cochlear EH. (B) Duration of symptoms and grade of vestibular EH. (C) Degree of hearing loss and grade of vestibular EH. (D) Degree of hearing loss and grade of cochlear EH.

develop fluctuating aural symptoms or MD in the contralateral ear in the future.[24] Our study found that EH was shown on MRI in all patients with clinically "definite MD" or MD-VM overlap syndrome, but only 38% of patients with clinically "probable MD" and 25% of patients with isolated cochlear symptoms. Imaging findings correlated with the symptomatic side(s) in 98% of patients in the "definite MD" group, 87% of patients shown to have EH in the "probable MD" group, and 66% of patients in the "isolated cochlear symptoms" group.

Vestibular Migraine and MD-VM Overlap Syndrome

More complex, perhaps, is the group of patients whose symptoms do not fit the classical diagnostic criteria for MD. This may be for several reasons, including but not limited to: patients not spontaneously reporting accompanying auditory symptoms with vertigo and vice versa; episodes of vertigo lasting <20 minutes; patients who do not have simultaneous or fluctuating auditory symptoms during attacks of vertigo due to profound hearing loss or a "dead ear"; and the coexistence of headaches and migraines with Ménièriform symptoms in the absence of typical fluctuating hearing loss due to profound deafness, leading to a misdiagnosis of VM.[25] Additionally, a patient can fulfill the criteria for both MD and VM, making it difficult to ascertain the correct diagnosis.[17] Headache, albeit with features not usually suggestive of migraine, has been shown to be highly prevalent in patients with a diagnosis of MD and is often associated with the vertigo attacks.[25] Oh et al[11] reported radiological evidence of cochleovestibular EH in 25% of patients with definite or probable VM with overlapping MD features. It was not clear whether these findings were attributable to the VM or MD part of the underlying pathology. Vestibular migraine with Ménière's disease overlap syndrome represented 25% of our study population, and all of this group were found to have radiological EH. In our study, the grade of vEH was higher in the MD-VM group compared to the MD group, although that of cEH was not significantly different.

Disease Duration and Severity of Hearing Loss

Our study found a statistically significant correlation between EH and increased duration of symptoms, as well as the severity of hearing loss. This is consistent with the findings of several other published studies. De Pont et al[26] demonstrated these findings in a retrospective study of 215 patients who had delayed IV-Gd-enhanced 3D FLAIR MRI. In an early study of just 34 patients who underwent 3D FLAIR MRI 24 hours after IT-Gd injection, Gürkov et al[27] found a significant correlation between EH and worse hearing thresholds. In a study of 50 patients with MD who underwent 3D FLAIR 24 hours after IT-Gd, Yang et al[28] found that both vEH and cEH significantly correlated with the PTA threshold. In addition, histopathological examination of the temporal bones has shown increasing severity of EH in patients with a longer duration of symptoms and/or more severe hearing loss.[29]

CONCLUSION

Gadolinium-enhanced MRI of the inner ears, increasingly with IV rather than IT injection, has gained popularity over the past decade. The improvement in MRI sequences and the development of more convenient techniques that are less invasive and time-consuming have, over time, enabled the transition from a predominantly research technique to one that is applicable in clinical practice. Our study reports the results from the first 100 patients scanned at our center within a clinical rather than research setting. Our results concord with previously published data that EH MRI (in our case using 4-hour-delayed IV-Gd-enhanced 3D-real IR MRI) is highly sensitive and specific for the detection of EH in patients who are diagnosed clinically with definite MD. The sensitivity is much lower for probable MD, but the specificity remains high. As with many other studies, it also found a statistically significant correlation between EH and the duration and severity of hearing loss. The grade of vEH might be higher in the MD-VM overlap syndrome group compared to the MD group, whereas that of cEH might be similar in both groups.

It is hoped that these imaging techniques will be particularly useful for patients being considered for interventions such as IT steroids or surgery. It is also possible that, in the future, objective imaging markers may be used to provide prognostic information to patients suffering from this potentially debilitating disease.

As with almost all of the other published studies, we acknowledge that there is a potential bias in our study, in particular, due to the non-blinding of the reporting radiologists.[22] Due to ethical considerations around IV contrast, the study is also limited by a lack of control subjects or a "pure VM" comparator group. A further limitation of the study was the relatively small number of patients included; however, this was necessarily small due to the aim of performing an early evaluation of this newly implemented clinical service.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Since our study was based on retrospective data from electronic medical records, ethical approval was not required. No patient-identifiable information was included.

Informed Consent: Since this is a retrospective study, a written informed consent from patients was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.K., J.A.; Design – J.A., H.K.; Supervision – H.K., C.A., Y.A; Materials – J.A.; Data Collection and/or Processing – J.A., Y.A., S.O., S.M., S.J.; Analysis and/or Interpretation – J.A., C.A., S.O., Y.A.; Literature Search – J.A., S.O.; Writing – J.A., C.A., S.O., S.J.; Critical Review – J.A., C.A., H.K., S.O.

Declaration of Interests: The authors have no conflicts of interest to declare.

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