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Original

Variations in the Formation of Lamellar Macular Hole through Epiretinal Membrane, Macular Pseudohole, and ERM-Foveoschisis

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Purpose: To investigate morphological changes associated with lamellar macular hole (LMH).
Methods: We retrospectively reviewed data for all eyes with LMH, as determined by spectral-domain optical coherence tomography (OCT), from patients who had undergone vitrectomy and had at least 12 months of preoperative and 6 months of postoperative follow-up data. Eyes were classified as those with morphological changes in the epiretinal membrane (ERM), macular pseudohole (MPH), or ERM-foveoschisis (ERM-FS) that were observed before LMH formation (group A), and those in which LMH was present at the first visit and remained unchanged until surgery (group B). Follow-up time (from first visit to surgery), time from detection of diseases associated with LMH, and morphological changes were analyzed.
Results: Of 14 eyes of 14 patients, 9 were in group A and 5 were in group B, and mean follow-up time was 49.2 ± 23.5 months and 44.4 ± 25.4 months in groups A and B, respectively. In group A, LMH formed through ERM in 1 eye, MPH in 2 eyes, and ERM-FS in 6 eyes; 5 eyes maintained LMH morphology for longer than 12 months. The mean time from associated disease to LMH was 11.2 ± 13.8 months, and 30.3 ± 25.5 months from LMH to surgery. BCVA significantly improved in group A ($p<0.05$) but not in group B ($p=0.0579$). Neither time to surgery in group A nor follow-up time correlated with postoperative BCVA.
Conclusion: LMH likely forms through progression of associated diseases, and time from LMH to surgery was not significantly associated with visual outcomes.
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Keywords: epiretinal membrane, lamellar macular hole, macular pseudohole, optical coherence tomography, vitrectomy

Introduction

Hubschman et al.[1] recently established a consensus definition for optical coherence tomography (OCT) characteristics and clarified the diagnostic factors for macular pseudohole (MPH), ERM-foveoschisis (ERM-FS), and lamellar macular hole (LMH). In this classification, cases previously described as tractional LMH are now categorized as ERM-FS, whereas those described as degenerative LMH are redefined as LMH. The definition of LMH is based on three mandatory criteria: (1) irregular foveal contour (abnormal, non-linear shape of the foveal pit contour), (2) foveal cavity with undermined edges, and (3) presence of at least one other sign evoking loss of foveal tissue, that is, pseudo-operculum, thinning of the fo-

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veal at its center, or in the area around the center.

In the present study, LMH was differentiated from ERM-FS on the basis of updated OCT criteria by Hubschman et al.[1], in which a foveal cavity with undermined edges, indicating presumed tissue loss, is required for LMH, while ERM-FS is characterized by retinal schisis without definitive tissue loss. We previously reported clinical and OCT findings of these associated diseases[2–4]. However, the mechanisms and pathways associated with LMH formation remain unclear. Lee et al.[5] investigated the developmental pathways of idiopathic LMH and identified four types of tractional progression. Bringmann et al.[6] also investigated the tractional development and morphological alterations of LMH and suggested that LMH may be associated with the results of the retinal wound repair process after tractional disruption.

Despite advances in OCT-based diagnostic criteria, the detailed morphological alterations that lead to LMH formation remain unclear. To date, no report has clearly described the relationship between LMH formation and its associated diseases. The present study thus investigated morphological changes during LMH formation.

Materials and Methods

This retrospective study was reviewed and approved by the Ethics Committee of Nippon Medical School (approval number: M-2023-161) in accordance with the ethical review processes at that institution[7]. Patients provided written consent for their information to be stored in the hospital's database and used for research purposes. This study was performed according to the principles of the Declaration of Helsinki.

Patient Data and OCT Analysis

We retrospectively reviewed the medical records of consecutive patients with LMH who had undergone vitrectomy between April 2020 and December 2023 and were followed for at least 12 months preoperatively and 6 months postoperatively. A diagnosis of LMH was based on spectral-domain (SD) OCT findings (Spectralis version 1.8.6.0, Heidelberg Engineering GmbH, Heidelberg, Germany) and updated criteria established by an international panel of vitreoretinal experts in 2020[1]. Horizontal and vertical 5-line B-scan images were obtained preoperatively and postoperatively. The anatomical features evaluated included the presence of retinal cysts, epiretinal proliferation (EP), disruption of the ellipsoid zone (EZ), foveal bump, and the hyperreflective stress sign. Inner and outer retinal cysts were defined as hyporeflective spaces in the inner nuclear layer and in Henle's fiber layer (HFL) and/or the outer plexiform layer, respectively. Disruption of the EZ was defined as an irregularity of the EZ line within a 1 mm diameter at the fovea. Foveal bump was defined as a bulge of retinal tissue in the foveal center. The hyperreflective stress sign was defined as a vertical hyperreflective line in the central fovea. Exclusion criteria included eyes with a history of prior vitreoretinal surgery (except mild cataract), other ophthalmic disorders, retinal vascular disease, uveitis, and trauma.

Visual Function Assessment

Best-corrected visual acuity (BCVA) was measured using a standard Japanese decimal visual acuity chart at a distance of 5 meters. For statistical analyses, decimal values were converted to the logarithm of the minimal angle of resolution (logMAR) units.

Surgical Procedures

All patients under local anesthesia underwent 25-gauge pars plana vitrectomy performed by two vitreoretinal surgeons (F.O., Y.M.). We injected 0.1 to 0.2 mL of 0.025% brilliant blue G solution gently over the macula, which was washed out with irrigation solution. After the ERM was peeled, 0.1 mL of brilliant blue G solution was applied to the macular area. We then completely peeled the remaining internal limiting membrane for eyes without EP. For patients with EP, we used the inverted internal limiting membrane flap technique with embedding of the EP into the fovea. After removing the lens by phacoemulsification, an intraocular lens was implanted when required, followed by vitrectomy.

Statistical Analysis

Mean values and standard deviations were calculated for follow-up time, age, and preoperative and postoperative BCVA. Differences between preoperative and postoperative BCVA were analyzed by Wilcoxon's signed-rank test. Spearman's rank correlation test was used to assess the correlation between preoperative and postoperative BCVA, as well as correlations of postoperative BCVA with time from LMH formation to surgery and time from the first visit to surgery. All statistical tests were considered significant at $p<0.05$. All analyses were carried out using SPSS Statistics (version 29.0, IBM).

Table 1A Demographics and clinical characteristics of patients with morphological changes

Patient No.	Age (years)	Pre-BCVA	Post-BCVA	Follow-up time (months)	Interval from other disorders to LMH (months)			Interval from LMH formation to surgery (months)
					ERM	MPH	ERM-FS	
1	64	0.000	–0.079	56	46	10	3	10
2	70	0.097	0.000	77		12		65
3	66	0.398	0.523	69		66		3
4	75	0.398	0.046	71			15	56
5	51	0.222	0.000	61			2	59
6	76	0.000	–0.079	25		12	12	13
7	69	0.222	0.155	49		1	1	38
8	76	0.097	–0.079	24		3	3	21
9	68	1.097	0.046	12		10	10	2
Mean ± SD	68.3 ± 7.8	0.281 ± 0.34	0.059 ± 0.19	49.2 ± 23.5				29.7 ± 25.2

BCVA: best corrected visual acuity, ERM: epiretinal membrane, MPH: macular pseudohole, ERM-FS: epiretinal membrane-foveoschisis, LMH: lamellar macular hole.

Table 1B Demographics and clinical characteristics of patients without morphological changes

Patient No.	Age (years)	Pre-BCVA	Post-BCVA	Interval from first visit to surgery (months)
1	71	0.398	0.301	41
2	70	0.115	–0.079	39
3	62	0.115	–0.079	12
4	70	0.523	0.301	83
5	78	0.155	0.000	47
Mean ± SD	70.2 ± 5.7	0.277 ± 0.17	0.089 ± 0.20	44.4 ± 25.4

BCVA: best corrected visual acuity.

Table 2A Preoperative and postoperative optical coherence tomography findings for patients with morphological changes

Patient No.	Inner cyst	Outer cyst	EZ disruption	EP	Foveal bump	Hyperreflective stress sign
	pre/post	pre/post	pre/post	pre	pre	pre
1	–/–	–/–	–/–	–	+	+
2	–/–	+/+	+/+	–	–	–
3	–/–	–/–	+/+	+	–	–
4	+/–	+/+	–/–	+	–	–
5	–/–	+/–	–/+	+	+	–
6	–/–	+/–	+/+	+	–	–
7	–/–	+/+	+/+	+	+	+
8	–/–	+/–	–/–	–	+	+
9	–/–	+/–	–/–	–	–	–

Results

Data from 14 eyes of 14 patients (8 males and 6 females) were analyzed. LMH developed via different pathways, including in 1 eye via ERM, MPH, and ERM-FS; in 2 eyes via MPH; in 2 eyes via ERM-FS; and in 4 eyes via both MPH and ERM-FS (**Table 1A**; Group A: Patients 1; 2 and 3; 4 and 5; and 6–9, respectively). In addition, 5 eyes maintained LMH morphology for longer than 12 months before undergoing surgery (**Table 1B**; Group B: Patients 1–5). There was no significant correlation between time from LMH formation to surgery in group A and postoperative BCVA (p=0.78). Similarly, time from first visit to surgery in group B was not significantly correlated with postoperative BCVA (p=0.72). **Table 2** sum-

Table 2B Preoperative and postoperative optical coherence tomography findings for patients without morphological changes

Patient No.	Inner cyst pre/post	Outer cyst pre/post	EZ disruption pre/post	EP pre	Foveal bump pre	Hyperreflective stress sign pre
1	−/−	−/−	−/+	+	−	+
2	+/−	+/−	−/−	+	+	−
3	−/−	−/−	−/−	−	−	−
4	−/−	−/−	−/−	−	+	−
5	−/−	+/−	−/−	−	−	−

EP: epiretinal proliferation, EZ: ellipsoid zone.

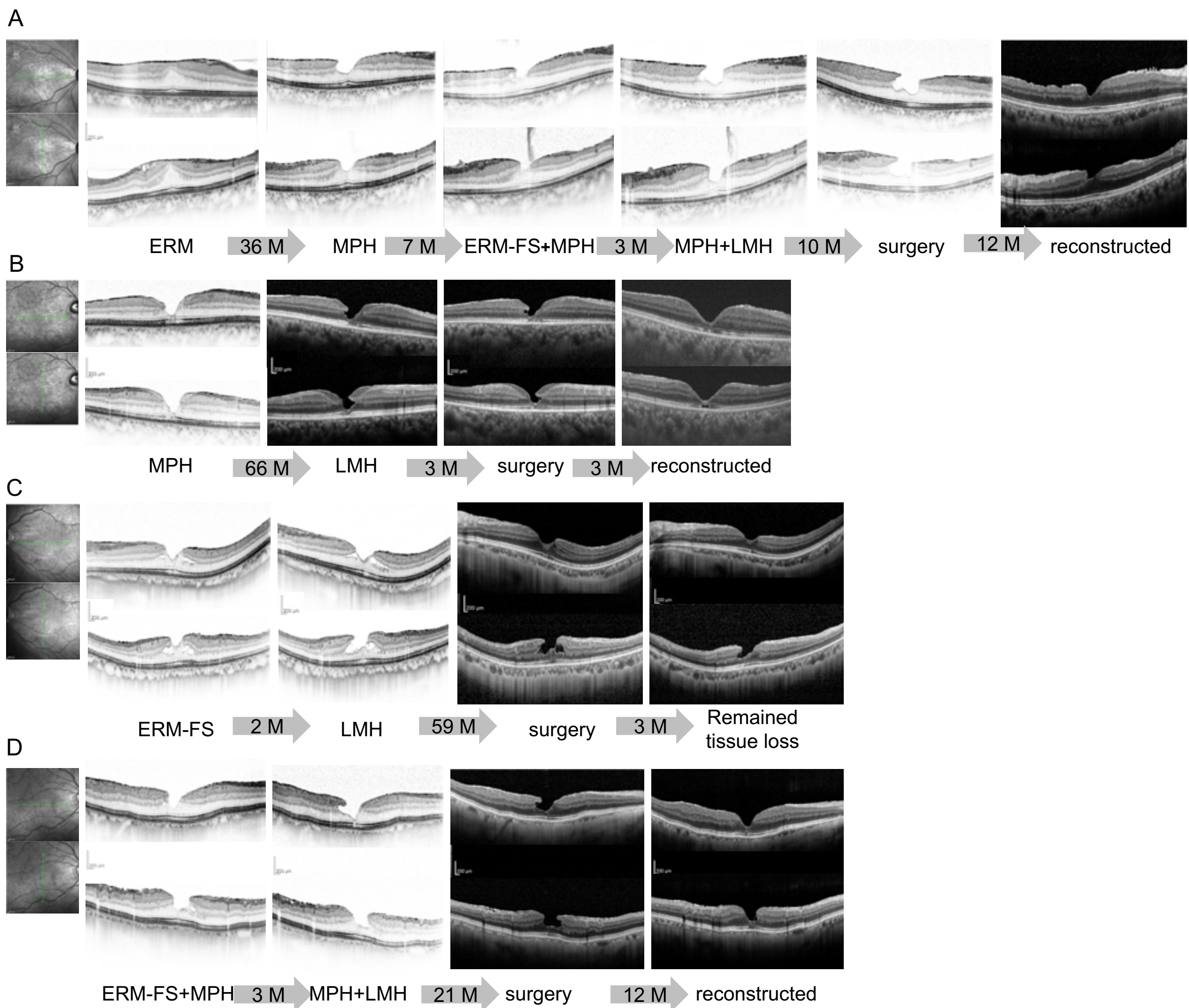

Figure 1 Representative cases of lamellar macular hole formation and morphological changes over time
(A), Images from Patient 1 in Table 1A showing sequential development through ERM, MPH, and ERM-FS. (B) and (C), Images from Patients 3 and 5 in Table 1A showing development from MPH and ERM-FS, respectively. (D), Images from Patient 8 in Table 1A showing development from both MPH and ERM-FS.

marizes preoperative and postoperative OCT findings for the eyes in groups A and B. Patient numbers in **Tables 1 and 2** correspond to each other. EZ disruption and EP were more frequent in eyes with morphological changes.

Figure 1 shows representative cases of the time course for OCT changes before LMH formation. Images in **Figure 1A** correspond to Patient 1 in **Table 1A** and show sequential development from ERM, to MPH, to ERM-FS.

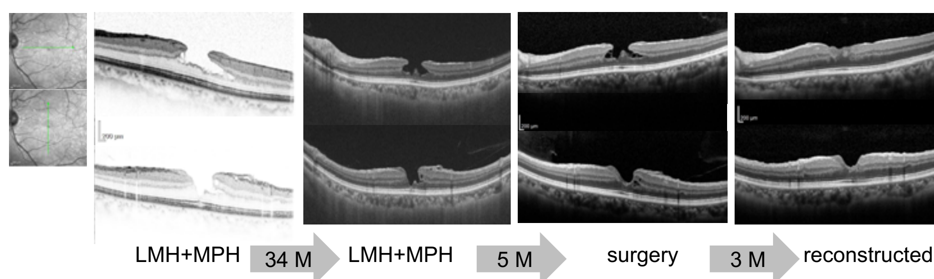

Figure 2 Representative case of lamellar macular hole without dynamic morphological changes during 12 months of follow-up
Images for Patient 2 in Table 1B showing LMH formation at the first visit.

Images in **Figure 1B and 1C** correspond to Patients 3 and 5 in **Table 1A** and show the development from MPH and ERM-FS, respectively. Images in **Figure 1D** correspond to Patient 8 in **Table 1A** and show development from both MPH and ERM-FS. In the patient in **Figure 1A**, LMH developed sequentially over 45 months, starting from ERM to MPH (36 months), followed by MPH to ERM-FS (7 months), and then ERM-FS to LMH (2 months). ERM was present at the first visit, and MPH, ERM-FS, and LMH developed in sequence. Although a hyperreflective stress sign was observed after posterior vitreous detachment (PVD), it was less apparent at the time of surgery. After PVD, MPH developed and ERM-FS appeared, which was likely due to ERM traction. Three months later, tissue loss was noted at the foveoschisis site, resulting in LMH formation. Surgery was performed at 10 months after LMH formation, at which point OCT showed a foveal bump and progressive tissue loss. Tissue loss appeared to continue after ERM-FS formation. EP was not observed during follow-up. After surgery, the foveal contour was reconstructed. The patient in **Figure 1B** underwent surgery at 3 months after LMH diagnosis, and the foveal contour was reconstructed after surgery. This patient exhibited EP and disruption of both the EZ and an interdigitation zone. EP and outer retinal layer disruption were present at the initial visit and gradually worsened. Although the tissue loss was reconstructed after surgery, disruption of the EZ and interdigitation zone remained. In **Figure 1C**, ERM-FS was present at the initial visit. Tissue loss occurred at the level of the HFL, which corresponded to the schisis area of ERM-FS. The interval between LMH diagnosis and surgery was 59 months. Three months after surgery, the irregular foveal contour persisted. In the patient in **Figure 1D**, MPH and ERM-FS were present before LMH formation. In this eye, the schisis area progressed to tissue loss over time. However, in some cases, such as the patient in **Figure 1C**,

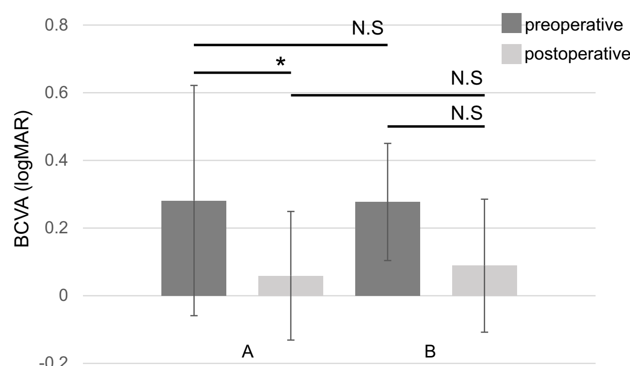

Figure 3 Preoperative and postoperative best-corrected visual acuity (BCVA) in groups A and B
BCVA was significantly better postoperatively in Group A but not in Group B.

LMH developed without apparent schisis formation at the HFL level. A hyperreflective stress sign was observed, and the foveal contour was reconstructed after surgery. **Figure 2** shows a representative case of LMH. Images are from Patient 2 in **Table 1B**, in whom an LMH was present from the initial visit. The interval between LMH diagnosis and surgery was 39 months. Three months after surgery, the irregular foveal contour was reconstructed. **Figure 3** shows preoperative and postoperative BCVA values in groups A and B. BCVA was significantly improved postoperatively in group A (p=0.044) but not in group B (p=0.058). **Figure 4** shows the correlation of preoperative with postoperative BCVA in all eyes (**Figure 4 A**), group A (**Figure 4B**), and group B (**Figure 4C**). Correlations were significant in all analyses (p=0.0003, p=0.007, and p=0.047, respectively).

Discussion

This is the first study to use OCT to document longitudinally the stepwise morphological progression from associated macular disorders, ie, ERM, MPH, and ERM-FS to LMH. Our findings provide new insights regarding the

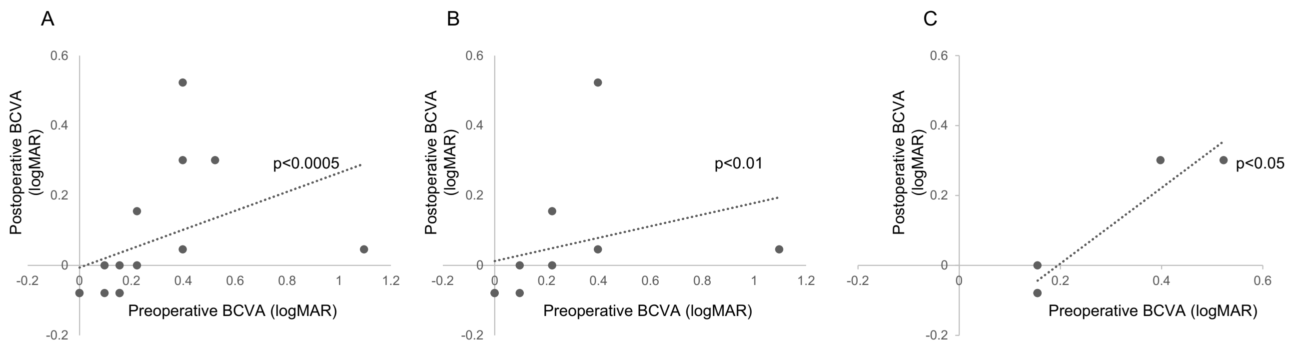

Figure 4 Correlation between preoperative and postoperative best-corrected visual acuity (BCVA) in all eyes (A), group A (B), and group B (C)
Preoperative and postoperative BCVA were significantly correlated in all analyses.

pathogenesis of LMH. In most cases, LMH was diagnosed and surgery was performed without notable dynamic morphological changes. However, some eyes in this study exhibited progressive morphological changes during the interval from follow-up until surgery.

Previous studies, such as the study by Matoba et al.[8], reported that the prevalence of mixed types of MPH, ERM-FS, and LMH was relatively high. However, to our knowledge, the present study is the first to document the morphological transition from these associated diseases to LMH. Our findings suggest that ERM, MPH, and ERM-FS progress to LMH, which highlights the importance of appropriate follow-up intervals to monitor such changes.

On the basis of our findings, we propose broadly classifying LMH into 2 distinct subtypes depending on the developmental pathway: one originating from MPH and the other from ERM-FS. These subtypes appear to differ not only in pathogenesis but also in structural vulnerability, the timing of tissue loss, and possible surgical outcomes.

In most of the present eyes, ERM-FS preceded LMH formation, and tissue loss occurred at the schisis area at the level of the HFL. The hyperreflective bridges of tissue may correspond to the stretched and verticalized Müller cell bodies and could potentially intermingle with the hyporeflective intraretinal spaces. Furthermore, these could be damaged over time and eventually develop into a foveal cavity. Traditionally, visual outcomes have been worse for LMH than for its associated conditions, such as MPH and ERM-FS[9,10]. This suggests that LMH is a clinical entity distinct from MPH and ERM-FS.

In 2 cases of MPH that progressed to LMH, the initially steep foveal contour gradually transformed into an irregular foveal contour, with 1 case exhibiting EP near the fovea. In cases of ERM-FS progression to LMH, the bridging structures observed at the HFL schisis area, which likely represent stretched Müller cells, gradually disappeared, lead to cavitation and LMH formation. With the exception of 1 case, macular morphology improved postoperatively, with the undermined foveal changes resolving after surgery. These observations suggest that progressive mechanical stress may disrupt Müller cell function, which plays a key role in maintaining foveal structural stability. Loss of Müller cell–mediated support may ultimately result in focal retinal tissue loss and undermined foveal changes, leading to LMH development. Recent evidence indicates that alterations in Müller cell trophism and pathology may contribute to retinal tissue degeneration and could represent a potential therapeutic target in retinal diseases[11].

Although surgery was performed more than 12 months after LMH formation in 7 of 9 patients, BCVA improved in these cases. Additionally, there was no significant correlation with the interval between LMH formation and surgery. Purtskhvanidze et al.[12] reported that LMH often remains stable for a prolonged period and that surgery should be considered in cases with significant visual loss or functional and morphological progression. The present study revealed a strong correlation between preoperative and postoperative BCVA. These findings suggest that better visual outcomes would be achieved if surgical interventions were guided primarily by visual acuity rather than by duration of observation.

This study had some limitations. First, it was a retrospective study that only included surgical cases. Second, the small sample size may have affected the results. Third, the follow-up duration varied, which may have limited the accuracy in determining the timing of morphological changes.

In summary, the present results document the dynamic morphological progression from associated macular diseases to LMH. Our findings suggest that LMH commonly develops through precursor conditions such as ERM, MPH, and ERM-FS and that the timing of surgical intervention should be guided by functional rather than temporal factors. Confirmation of these hypotheses will require prospective studies with larger sample sizes.

Author Contributions: FO designed the study and supervised the project. YN, HG, YM, KM, TK, and NK collected data. NK prepared the manuscript. All authors critically reviewed the manuscript and approved the final version for submission. The guarantor of the article is NK.

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Conflict of Interest: None declared.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: The authors declare that no generative AI or AI-assisted technologies were used in writing, revising, or preparing figures for this manuscript.

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