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Clinical characteristics and treatment outcomes of bilateral myopic macular neovascularization in high myopic patients

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Abstract

Purpose: To evaluate the clinical features and treatment outcomes of bilateral myopic macular neovascularization (mMNV).

Methods: This single-centre retrospective study included patients with bilateral high myopia who were newly diagnosed with unilateral mMNV (first eye) between January 2008 and July 2020. Patients who presented with mMNV or macular atrophy suggestive of previous mMNV in the fellow eye (second eye) were excluded. Patients were classified into unilateral or bilateral groups based on mMNV development in the second eye during follow-up of >36 months.

Results: Ninety-three patients were included with the mean age of 55.4 ± 13.1 years and 71 (76.3%) were female. The mean baseline spherical equivalent was −13.0 ± 5.5 diopters. Of total, 21 (22.6%) developed mMNV in the second eye during the mean follow-up period of 95.1 ± 38.9 months; the cumulative probabilities were 16.2% at 5 years and 28.9% at 10 years after the first eye mMNV development. The uninvolved second eyes of the unilateral group had shorter axial length (AL) and greater subfoveal choroidal thickness than the eyes with mMNV. The unilateral group showed a greater interocular difference in AL than the bilateral group ($p < 0.001$). The presence of lacquer cracks in the second eye was identified as a significant risk factor for the second eye mMNV development (HR = 5.64, 95% CI: 1.59–20.08, $p = 0.008$). In the bilateral group, the second eye showed less vision improvement after anti-VEGF treatment, but the final visual acuity and cumulative probability of fovea-involving mMNV-related chorioretinal atrophy did not differ between the eyes.

Conclusions: Approximately 30% of bilateral high myopic patients with unilateral mMNV are estimated to develop mMNV in the second eye over a period of 10 years. The presence of lacquer cracks in the second eye was a significant risk factor. The first and second eyes showed comparable treatment outcomes.

KEYWORDS

axial length, bilateral high myopia, chorioretinal atrophy, Lacquer crack, myopic macular neovascularization, pathologic myopia anti-VEGF

1 | INTRODUCTION

High myopia is one of the leading causes of irreversible vision loss worldwide; this is especially relevant in East Asia, where the prevalence of myopia is increasing (Wong & Saw, 2016). In patients with high myopia, visual impairment usually results from pathologic changes in the macula, including myopic maculopathy, retinoschitic changes and myopic macular neovascularization (mMNV), as well as other ocular complications such as rhegmatogenous retinal detachment, glaucoma and cataract (Leveziel et al., 2020; Sankaridurg et al., 2021; Ye et al., 2022; Yoshida et al., 2003). Among these, mMNV, which occurs in 5.2%–16.0% of individuals

with pathologic myopia, is the main vision-threatening complication (Fang et al., 2018; Wong et al., 2014). A thinner choroid, higher grade of myopic maculopathy and the presence of lacquer cracks (LCs) have been reported as factors associated with the development of mMNV (Cheung et al., 2013; Ikuno et al., 2008, 2010; Ohno-Matsui et al., 2003). If untreated, mMNV lesion regresses, leaving a pigmented fibrovascular scar, also called Fuchs spot, and an area of fovea-involving mMNV-related chorioretinal atrophy (CRA), which is characterized by gradual fovea-centred centrifugal enlargement that eventually results in irreversible central vision loss in more than 90% of patients (Yoshida et al., 2003).

Axial length (AL) shows a strong interocular correlation in individuals (Hecht et al., 2024), and high myopia mostly presents bilaterally. Complications of pathologic myopia, such as myopic macular degeneration, myopic traction maculopathy and mMNV in one eye, are also predictive of similar complications in the contralateral eye (Li et al., 2024), indicating symmetry between the eyes for myopic complications. However, only a limited number of studies assessed the clinical features of bilateral mMNV, particularly its therapeutic response and long-term prognosis. In this study, we investigated the clinical characteristics and risk factors associated with bilateral mMNV development. In addition, we compared the outcomes of anti-vascular endothelial growth factor (VEGF) treatment, in terms of visual acuity and the incidence of fovea-involving mMNV-related CRA between the first and second eyes with mMNV.

2 | MATERIALS AND METHODS

2.1 | Patients

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. 2003-231-1115) and adhered to the tenets of the Declaration of Helsinki. The medical records of patients with bilateral high myopia who were newly diagnosed with unilateral mMNV between January 2008 and July 2020 and followed up for ≥36 months were reviewed. High myopia was defined by AL ≥26.0 mm and/or refractive errors < −6.0 diopters in spherical equivalent (SE). The exclusion criteria were as follows: (1) a history of any treatment for mMNV including anti-VEGF, laser photocoagulation and photodynamic therapy; (2) absence of high myopia in the contralateral eye; (3) presence of mMNV in both eyes at the first presentation; (4) presence of a macular atrophic scar change suggestive of previous mMNV in any eye; (5) history of intraocular surgery other than cataract extraction; and (6) history of other ocular disorders, such as age-related macular degeneration, retinal vascular diseases, retinal detachment, central serous chorioretinopathy, intraocular inflammatory diseases including punctate inner choroidopathy and multifocal chorioretinitis, and glaucoma.

2.2 | Ophthalmic examinations

All patients underwent a thorough ophthalmic evaluation, including best-corrected visual acuity (BCVA), refractive error and intraocular pressure measurements, slit-lamp examination and dilated fundus examination. Ocular laboratory examinations included colour fundus photography, ultra-widefield retinal imaging (Optos California, Optos, PLC, Dunfermline, UK), AL measurements using IOL Master 700 (Carl Zeiss Meditec Inc., Jena, Germany) and spectral-domain optical coherence tomography (SD-OCT) using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) or Cirrus OCT (Carl Zeiss Meditec, Dublin, CA, USA). Fluorescein angiography (FA) was performed using a fundus camera (TRC-50DX; Topcon, Tokyo, Japan), and indocyanine green angiography (ICGA) was performed using a confocal scanning laser ophthalmoscope (HRA-2; Heidelberg Engineering, Heidelberg, Germany).

The presence of MNV in the first eye at the initial presentation and the contralateral eye during follow-up was confirmed on the basis of the presence of well-defined hyperfluorescence in the early phase with leakage in the late phase on FA and corresponding hyperreflective subretinal lesions with or without subretinal fluid on SD-OCT (Cheung et al., 2017; Ohno-Matsui et al., 2018). The location of mMNV was considered subfoveal when the choroidal neovascularization (CNV) was located under the centre of the fovea, juxtafoveal when the edge of CNV was located within 200 μm from the foveal centre, and extrafoveal when the distance between the CNV edge and foveal centre was more than 200 μm. According to the Meta-analysis of Pathologic Myopia (META-PM) Study Group classification, myopic macular degeneration was classified as follows: category 1, tessellated fundus; category 2, diffuse CRA; category 3, patchy CRA; and category 4, macular atrophy (Ohno-Matsui et al., 2015). Using the ultra-widefield retinal images, the presence and type of posterior staphyloma (PS) were determined according to Ohno-Matsui's classification system: wide macular, narrow macular, peripapillary, nasal, inferior and others (Ohno-Matsui, 2014). An LC was defined as a fine and irregular yellowish linear lesion at the macula. Subfoveal choroidal thickness (SCT) was measured manually using a calliper as the subfoveal perpendicular distance between the Bruch membrane and the sclera–choroidal junction in the OCT scan image.

2.3 | Treatment and follow-up

After diagnosis of mMNV, patients were treated with intravitreal injections of anti-VEGF agents, including 1.25 mg bevacizumab (Avastin; Genentech Inc., San Francisco, CA), 0.5 mg ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) or 2.0 mg aflibercept (Eylea, Bayer HealthCare, Leverkusen, Germany). None of the patients were treated with other methods, such as laser photocoagulation and photodynamic therapy. Treatment with the anti-VEGF agent was initiated with either three monthly loading injections or a single

injection, and the choice of the anti-VEGF agent and number of loading injections were based on the treating physician's discretion. Retreatment was administered on an as-needed basis when the patient showed any of the following signs of recurrence of mMNV: (1) reappearance of intra- and/or subretinal fluid on OCT, (2) fuzziness and increase in the size of mMNV on OCT, (3) new macular haemorrhage from the mMNV lesion or (4) reappearance of leakage on FA. Patients were examined monthly after treatment, and the visit interval was adjusted according to disease activity.

2.4 | Data analysis

Eyes with mMNV at baseline were designated as the *first eye*, whereas contralateral eyes without mMNV at baseline were designated as the *second eye*. Patients who developed mMNV in the second eye during follow-up were classified into the bilateral group and those who did not were classified into the unilateral group. The first eye with mMNV and the second eye without mMNV in the unilateral group were designated as U1 and U2, respectively, while the first and second eyes with mMNV in the bilateral group were designated as B1 and B2, respectively. Baseline demographic factors and ocular characteristics were compared between the two groups. Two independent retinal specialists (SHL and CKY) performed the qualitative grading (META-PM categorization, PS classification and presence of LCs) and SCT measurements. Any discrepancies were adjudicated by a third retinal specialist (UCP), and measurements from the two graders were averaged for statistical analysis. In the bilateral group, the treatment outcomes in the first and second eyes were compared in terms of BCVA changes and the development of fovea-involving mMNV-related CRA.

To evaluate clinical and ocular characteristics, student *t*-test and Mann–Whitney *U* test were used to compare continuous variables, while the chi-square test and Fisher's exact test were used for categorical variables. Kaplan–Meier analysis was performed to describe the development of mMNV in the second eye and the development of fovea-involving mMNV-related CRA in the bilateral group. Univariable and multivariable Cox proportional-hazard models were used to identify risk factors and calculate hazard ratios (HRs) for the development of mMNV in the second eye. All statistical analyses were performed using SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA), and *p*-values <0.05 were considered statistically significant.

3 | RESULTS

One hundred thirty-one patients met the inclusion criteria, of which 38 were excluded from the study: 10 patients with previous mMNV treatment history, 16 patients showing a macular atrophic scar changes at the first visit, one patient with bilateral mMNV at the first presentation, six patients who underwent a previous intraocular surgery other than cataract extraction and five patients with other ocular disorders, namely multifocal choroiditis and panuveitis, neovascular age-related macular degeneration and central serous chorioretinitis. As a result, a total of 93 patients with bilateral high myopia and unilateral mMNV were included in the analysis.

The patient demographics are shown in Table 1. The mean age at the diagnosis of mMNV in the first eye was 55.4 ± 13.1 years (range, 26–89 years), and the baseline SE was −13.0 ± 5.5 diopters. The mean follow-up period was 95.1 ± 38.9 months (range, 36–178 months). For the diagnosis of mMNV, FA or ICGA was performed in 81 of 93 patients (87.1%). During the follow-up period, 21 patients (22.6%) developed mMNV in the second eye and were classified into the bilateral group, and the remaining 72 patients (77.4%) were classified into the unilateral group. The mean age at mMNV development in the first eye and the sex distribution did not differ between the groups; however, patients in the bilateral group had a significantly longer follow-up period ($p=0.013$). The cumulative probability of mMNV development in the second eye was 1.1% at 1 year, 9.7% at 3 years, 16.2% at 5 years and 28.9% at 10 years after mMNV development in the first eye (Figure 1). The mean time interval between the diagnosis of mMNV in the B1 and B2 in the bilateral group was 49.0 ± 26.1 months (range, 8–86 months).

When clinical characteristics were compared between eyes within each group, the myopic macular degeneration grade was comparable between the eyes in both groups. However, the presence of PS at baseline was more frequent in U1 than in U2 in the unilateral group ($n=56/72$ [77.8%] vs. $n=41/72$ [56.9%]; $p=0.008$), whereas no inter-eye difference was observed between B1 and B2 in the bilateral group. In addition, the presence of LCs at baseline was more frequent in U1 than in U2 in the unilateral group ($n=63/72$ [87.5%] vs. $n=28/72$ [28.9%]; $p<0.001$), whereas no inter-eye difference was observed in the bilateral group. The mean AL and SCT were compared between the eyes, and the results are shown in Figure 2a,b, respectively. The mean AL of U1, U2, B1 and B2 were 29.73 ± 1.76, 28.80 ± 2.12, 30.37 ± 2.04 and 30.34 ± 2.15 mm, respectively. The AL of U2 was significantly shorter than those of U1, B1 and B2 ($p=0.009$, 0.001 and 0.014, respectively). Although the ALs of B1 and B2 were longer than that of U1, the differences were not statistically significant ($p=0.225$ and 0.252, respectively). Patients in the unilateral group showed a greater interocular difference in AL than those in the bilateral group (1.45 ± 1.27 mm vs. 0.52 ± 0.50 mm, $p<0.001$). At baseline, the mean SCTs of U1, U2, B1 and B2 were 59.9 ± 48.7, 83.7 ± 68.1, 51.1 ± 32.4 and 61.4 ± 38.8 μm, respectively. The SCT of U2 was significantly greater than those of U1 ($p=0.017$) and B1 ($p=0.003$), and marginally greater than that of B2 ($p=0.061$). In a manner similar to the trend in AL, the mean SE was significantly more myopic in the U1 group compared with the U2 group (−13.8 ± 5.0 D vs. −10.4 ± 5.0 D, $p=0.009$). By contrast, there was no significant difference in SE between the B1 and B2 groups (−16.1 ± 5.8 D vs. −14.5 ± 6.1 D, $p=0.553$).

A Cox proportional hazard model was used to evaluate the risk factors for mMNV development in the second eye, considering the varied follow-up periods among the patients. In the univariable model, the presence of an

TABLE 1 Baseline clinical characteristics of patients with unilateral and bilateral myopic macular neovascularization.

Parameters		Unilateral group			Bilateral group			*p*-value
Number of patients, *n* (%)		72 (77.4)			21 (22.6)			–
Follow-up period, months (*SD*)		89.8 (38.2)			113.5 (36.5)			0.013**
Female, *n* (%)		54 (75.0)			17 (81.0)			0.570*
Age at first eye diagnosis, years (*SD*)		56.4 (13.1)			52.1 (12.6)			0.186**
		First eye	Second eye	*p*-value	First eye	Second eye	*p*-value	
META-PM categories	1	36 (50.0%)	46 (63.9)	0.103*	10 (47.6%)	10 (47.6%)	0.693*	–
	2	16 (22.2%)	16 (22.2%)		6 (28.6%)	4 (19.0%)		
	3	20 (27.8%)	10 (13.9%)		5 (23.8%)	7 (33.3%)		
Posterior staphyloma	No staphyloma	16 (22.2%)	31 (43.1%)	0.072*	3 (14.3%)	3 (14.3%)	1.000*	–
	Wide macular type	48 (66.7%)	34 (47.2%)		15 (71.4%)	15 (71.4%)		
	Narrow macular type	6 (8.3%)	5 (6.9%)		3 (14.3%)	3 (14.3%)		
	Peripapillary type	1 (1.4%)	2 (2.8%)		0 (0%)	0 (0%)		
	Nasal type	0 (0%)	0 (0%)		0 (0%)	0 (0%)		
	Inferior type	1 (1.4%)	0 (0%)		0 (0%)	0 (0%)		
Lacquer crack	Present	63 (87.5%)	28 (38.9%)	<0.001*	18 (85.7%)	16 (76.2%)	0.348*	–
	Absent	9 (12.5%)	44 (61.1%)		3 (14.3%)	5 (23.8%)		
mMNV location	Subfoveal	47 (65.3%)	NA	NA	15 (71.4%)	16 (76.2%)	0.726*	–
	Juxtafoveal	25 (34.7%)	NA		6 (28.6%)	5 (23.8%)		
	Extrafoveal	0 (0%)	NA		0 (0%)	0 (0%)		
Axial length, mm (*SD*)		29.73 (1.76)	28.80 (2.12)	0.009**	30.37 (2.04)	30.34 (2.15)	0.972**	–
Spherical equivalent, D (*SD*)		−13.8 (5.0)	−10.4 (5.0)	0.009**	−16.1 (5.8)	−14.5 (6.1)	0.553	
Subfoveal choroidal thickness, μm (*SD*)		59.9 (48.7)	83.7 (68.1)	0.017**	51.1 (32.4)	61.4 (38.8)	0.356**	–
Number of intravitreal injection of anti-VEGF agent (*SD*)		3.7 (3.4)	NA	NA	4.5 (3.5)	3.0 (2.6)	0.113**	–

Abbreviations: D, diopter; META-PM, meta-analysis of pathologic myopia; mMNV, myopic macular neovascularization; NA, not applicable; *SD*, standard deviation; VEGF, vascular endothelial growth factor.

*p-values were derived using Pearson chi-squared test. **p-values were derived using student t-test.

LC in the second eye (HR = 4.512, 95% confidence interval [CI]: 1.649–12.348, $p = 0.003$), the presence of PS in the second eye (HR = 3.790, 95% CI: 1.116–12.873, $p = 0.033$) and greater AL in the second eye (HR = 1.332, 95% CI: 1.044–1.699, $p = 0.021$) showed significant associations. However, in the multivariable model, only the presence of an LC in the second eye was identified as a significant risk factor for mMNV development in the second eye during follow-up (HR = 5.643, 95% CI: 1.585–20.084, $p = 0.008$).

In the bilateral group, a subgroup analysis was performed to compare the prognosis of the first and second eyes after anti-VEGF treatment. Figure 3a shows the changes in BCVA after the first intravitreal anti-VEGF treatment in the first and second eyes of the bilateral group. At baseline, the first eyes had worse BCVA than the second eyes with borderline significance (1.01 ± 0.61 vs. 0.66 ± 0.51, $p = 0.052$), but BCVA during the follow-up did not differ between the eyes, including the final visits (0.85 ± 0.83 vs. 0.69 ± 0.60, $p = 0.492$). In the first eye, significant BCVA improvement from baseline was observed at 3, 6 and 12 months after the first injection ($p = 0.006$, 0.010 and 0.001, respectively) but not at the final follow-up visit. By contrast, the second eye showed no significant BCVA change from baseline at any time points. The incidence of fovea-involving mMNV-related CRA during follow-up in the first and second eyes was not significantly different ($n = 5/21$ [23.8%] vs. $n = 4/21$ [19.0%]; $p = 1.000$), and the cumulative probabilities of fovea-involving mMNV-related CRA development did not differ between the eyes (Figure 3b; $p = 0.638$, log-rank test).

An additional analysis was conducted on 24 (25.8%) of 93 eyes from U1 and B1 groups that showed a decrease of ≥3 lines in BCVA between the 12-month visit and the final follow-up, in order to identify the underlying causes of long-term vision loss. When multiple causes were assigned to a single eye, multiple recurrence (≥3) of mMNV was the most common cause (15 eyes, 62.5%), followed by fovea-involving CRA progression (14 eyes, 58.3%), fibrosis of mMNV (10 eyes, 41.7%) and the progression of META-PM category (8 eyes, 33.3%).

4 | DISCUSSION

The present study included patients with high myopia and unilateral mMNV who were followed over a mean period of 8 years, and the development of mMNV in fellow eyes occurred in 21 of the 93 patients (22.6%). The cumulative probability of the development of mMNV in the second eyes was 16.2% and 28.9% at 5 and 10 years, respectively. The uninvolved second eyes of patients with unilateral mMNV had shorter ALs and greater SCT than the eyes with mMNV in patients with unilateral and bilateral mMNV. The presence of LCs in the second eye was a significant risk factor for mMNV development

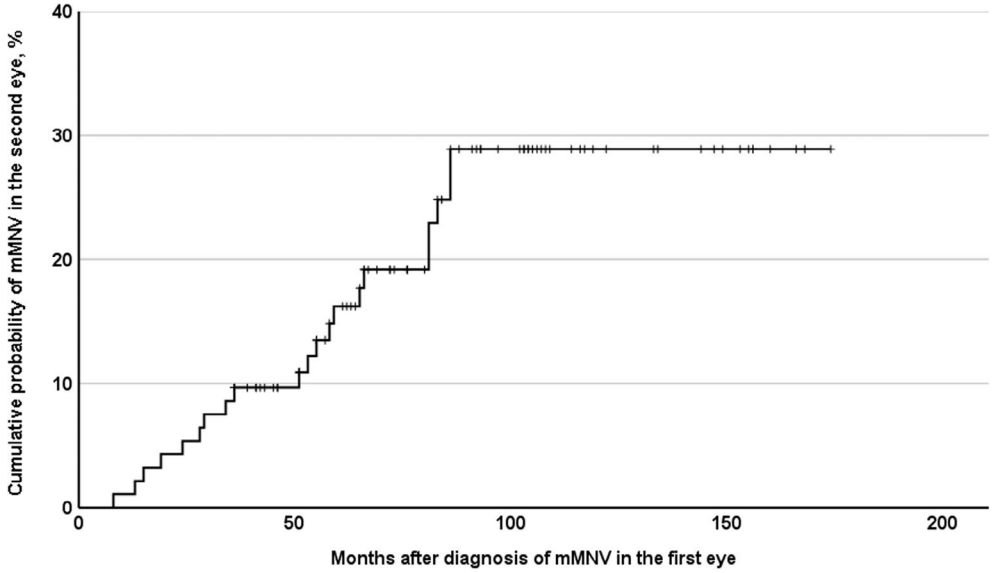

FIGURE 1 Cumulative probability of myopic macular neovascularization (mMNV) development in the second eye after diagnosis in the first eye.

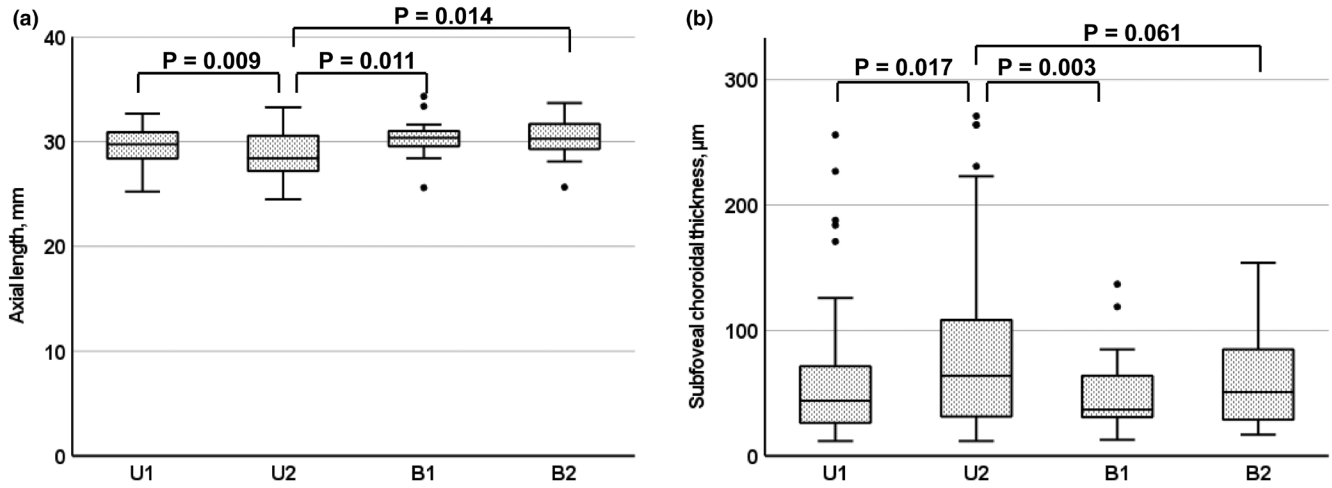

FIGURE 2 Axial length (a) and subfoveal choroidal thickness (b) in each eye of the unilateral and bilateral myopic macular neovascularization (mMNV) groups. U1, the first eye with mMNV in the unilateral group; U2, the second eye without mMNV in the unilateral group; B1, the first eye with mMNV in the bilateral group; B2, the second eye with mMNV in the bilateral group.

in the second eye. In patients with bilateral mMNV, the first and second eyes showed no significant difference in terms of visual acuity and the development of fovea-involving mMNV-related CRA after anti-VEGF treatment.

The incidence of mMNV has been reported to be 5.2%–16.0% in pathologic myopia (Fang et al., 2018; Wong et al., 2014), but research on the development of mMNV in uninvolved fellow eyes in patients with preexisting mMNV in only one eye is limited. In 2003, Ohno-Matsui et al. conducted a study with a mean follow-up period of 130.2 months and reported that the incidence of mMNV in fellow eyes of patients with unilateral mMNV was 34.8% (16 of 46 patients) (Ohno-Matsui et al., 2003) In a more recent study by Ravenstijn et al., conducted among individuals of European descent, mMNV development in the fellow eye was observed in 27% of the patients (24 of 88) with a mean interval of 48 months (Ravenstijn et al., 2023). The cumulative incidences were 21% at 5 years and 38% at 10 years. These results are comparable to those of the present study and suggest that the pattern of bilateral mMNV development is similar across different ethnic groups. In previous cross-sectional studies, the incidence of bilaterality of mMNV ranged from 15% to 23.3% (Leveziel et al., 2013; Wong et al., 2014), but the results from longitudinal follow-up studies, including those by Ravenstijn et al., Ohno-Matsui et al. and the present study, indicate that the lifetime incidence of bilateral involvement of mMNV is higher, and the second eyes in patients with unilateral mMNV require more attention (Figure 4).

The pathogenesis of mMNV is not yet fully understood, and various theories have been proposed, including those involving mechanical, vascular, systemic and genetic aetiologies (Cheung et al., 2013; Kim et al., 2011; Leveziel et al., 2012; Long et al., 2013). LCs, which are thought to represent mechanical breaks in the complex of retinal pigment epithelium (RPE)-Bruch

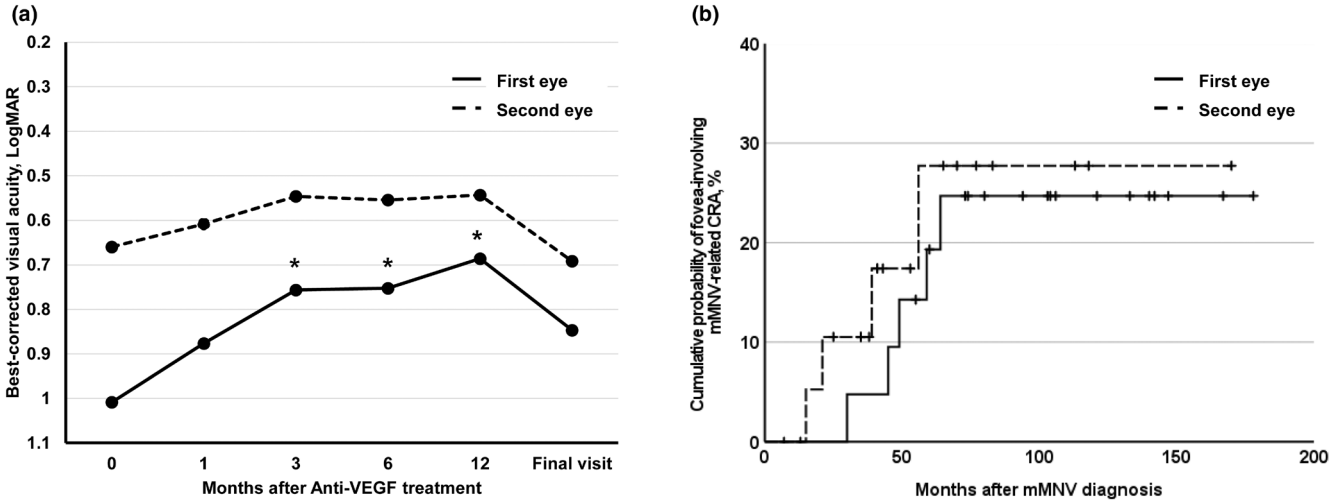

FIGURE 3 Treatment prognosis of the first and second eyes with myopic macular neovascularization (mMNV) in the bilateral group. (a) Kaplan–Meier survival curve showing cumulative probability of development of fovea-involving mMNV-related chorioretinal atrophy (CRA). (b) Change in the mean best-corrected visual acuity after anti-vascular endothelial growth factor (VEGF) treatment. Asterisks indicate significant change from baseline ($p<0.05$).

membrane-choriocapillaris due to elongation in highly myopic eyes, are well-known predisposing lesions of mMNV (Ohno-Matsui et al., 2003). In this study, the presence of an LC in the second eye was identified as the only risk factor for mMNV development in the second eye of patients with unilateral mMNV, indicating the role of mechanical factors in mMNV development. However, this may not necessarily indicate that new mMNV develops at the preexisting LC. Fine and irregular yellow lines in and around the macula, which are typical features of LCs, may represent healed scars of breaks in the RPE-Bruch membrane-choriocapillaris complex and are unlikely to trigger mMNV, whereas mMNV may develop through a relatively new break that is not yet healed or during the healing process (Ohno-Matsui et al., 2003, 2021). As a risk factor for mMNV, a preexisting LC in the second eye may simply imply persistent expansional stress at the posterior pole due to continuous axial elongation or staphyloma enlargement, which may lead to the formation of new breaks and eventually result in mMNV development. Further studies with better visualization of LCs are required to elucidate the association between mMNV development and LC chronicity in eyes with high myopia.

In this study, the second eye of the unilateral group, which did not develop mMNV during follow-up, had significantly lower AL and greater SCT at baseline than the other eyes with mMNV. Although these factors were not identified as risk factors for mMNV development in the second eye in the multivariable analysis, this finding suggests that less severe structural changes related to high myopia may protect against mMNV development. In particular, choroidal thinning has been reported as one of the major risk factors for mMNV in previous studies (Barteselli et al., 2014; Cheung et al., 2013; Ikuno et al., 2010) In eyes with high myopia, continuous choroidal thinning is believed to play an important role in the progression of myopic macular degeneration (Fang et al., 2019). Although the mechanism underlying this effect is still unclear, decreased choroidal circulation and perfusion may result in hypoxic changes in the outer retina and RPE, where VEGF is secreted via factors such as hypoxia-inducible factor-1 (Babapoor-Farrokhran et al., 2023).

In the subgroup analysis for patients with bilateral mMNV, although better outcomes were expected in the fellow eye due to increased patient awareness and more prompt presentation to ophthalmologic care, the second eye in this study did not show a statistically significant improvement in BCVA from baseline. This finding may be attributed to better visual acuity at the time of mMNV occurrence in the second eye, although the statistical significance was marginal. This could have resulted in a ceiling effect, limiting the extent of measurable visual gain. In addition, patients were 49.0 months older on average at the time of mMNV development in the second eye in comparison with that in the first eye, and this may have influenced treatment outcomes, since an older onset age is invariably reported to be an independent prognostic factor for worse treatment outcomes (Cheung et al., 2017; Gharbiya et al., 2012; Kojima et al., 2006; Milani et al., 2012; Ruiz-Moreno et al., 2010; Wong et al., 2014).

Although anti-VEGF treatment has revolutionized the treatment outcomes of mMNV, initial vision improvement achieved with anti-VEGF treatment usually tends to decline during follow-up over several years (Bae et al., 2022; Ruiz-Moreno et al., 2015; Sakata et al., 2023; Sarao et al., 2016). This usually occurs when mMNV-related CRA develops and enlarges to finally involve the foveal centre because this area is characterized by a lack of photoreceptors, RPE and choriocapillaris, resulting in absolute scotoma (Ohno-Matsui et al., 2016; Park et al., 2022). In the bilateral group in this study, the probability of fovea-involving mMNV-related CRA development during follow-up was comparable between the eyes. Thus, the long-term clinical course of mMNV in terms of CRA development may not be different between the first and second eyes, with both eyes experiencing a similar amount of vision deterioration between 12 months and the final visits.

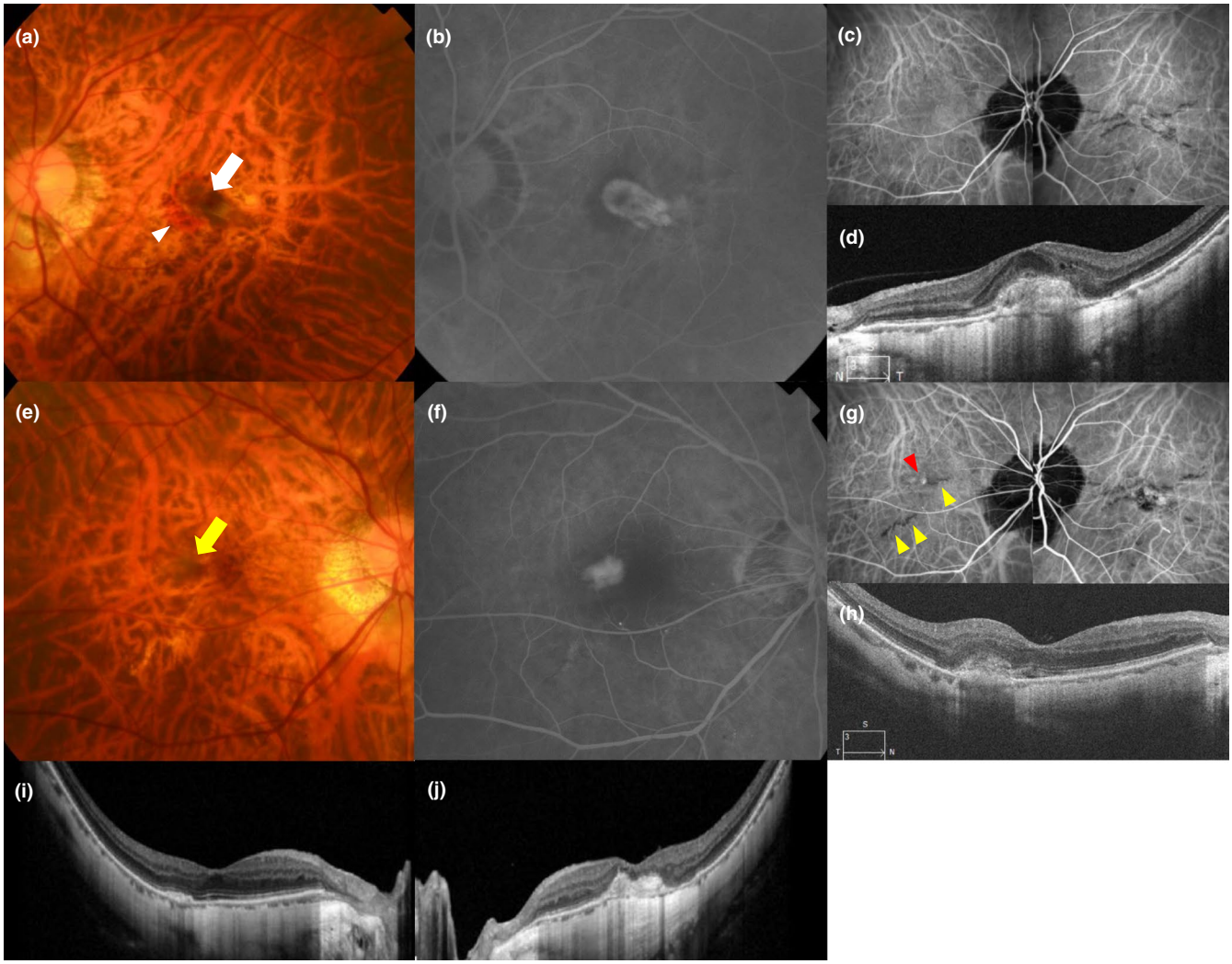

FIGURE 4 Representative case of a 60-year-old male with bilateral myopic macular neovascularization (mMNV), whose axial length was 30.03 mm in the right eye and 30.37 mm in the left eye. (a) At baseline, colour fundus photograph showed mMNV as greyish membrane (white arrow) and haemorrhage (white arrowhead) in the left eye. Best-corrected visual acuity (BCVA) in the left eye was 20/50. (b) Fluorescein angiogram (FA) showed hyperfluorescence with leakage. (c) Indocyanine green angiogram (ICGA) showed well-delineated hypofluorescent streaks corresponding to lacquer cracks and mMNV lesion as mild hyperfluorescence in the left eye, whereas there was no lesion in the right eye. (d) Optical coherence tomography (OCT) showed hyperreflective lesion corresponding to mMNV. He was treated with 12 intravitreal injection of bevacizumab or aflibercept during 30 months of follow-up due to recurrence of mMNV. (e, f) At 30 months after development of mMNV in the left eye, mMNV developed in his right eye (yellow arrow). BCVA in the left eye was 20/40. (g) ICGA showed new lacquer cracks (yellow arrowheads) and mMNV lesion as hyperfluorescence (red arrowhead). (h) OCT showed hyperreflective lesion corresponding to mMNV. He was treated with one intravitreal injection of aflibercept in the right eye but required four additional injections in the left eye during further follow-up. (i, j) At 81 months after development of mMNV in the left eye, OCT showed stable mMNV lesion in the left eye and no lesion in the right eye. BCVA was 20/40 in the right eye and 20/100 in the left eye.

In addition to its retrospective design and small cohort size, this study had several limitations. First, this study was limited to patients with bilateral high myopia to ensure a clearly defined cohort of mMNV. In East Asian populations, where the prevalence of myopia is high, CNV in eyes with mild to moderate myopia may also arise from heterogeneous aetiologies, such as idiopathic CNV. By restricting the study population to patients with high myopia, we tried to minimize the diagnostic ambiguity of mMNV, but this approach may have limited the generalizability of the results to eyes with less severe myopia. Second, although there may be a potential association between the activity of mMNV in the first eye and the risk of mMNV development in the fellow eye, detailed analyses regarding the location and morphological features of second mMNV in the first eye were not conducted. Third, the decision to perform anti-VEGF retreatment was made by different physicians, which could be a source of bias. Fourth, various anti-VEGF agents were used for intravitreal injections in this study, but their therapeutic efficacy for mMNV has been reported to be comparable (Cha et al., 2014; Wang et al., 2018; Zhu et al., 2016). Finally, the follow-up period for each individual differed, which may have interfered with the precise assessment of the incidence of fellow eye mMNV development. Although we have included patients with follow-up longer than 3 years, some patients with favourable outcomes following unilateral mMNV treatment might have been lost, whereas those who developed mMNV in the fellow eye were more likely to continue follow-up, leading to an overestimation of the incidence of fellow eye involvement and significantly longer follow-up period in the bilateral group.

In conclusion, this study demonstrated that a considerable proportion of high myopic patients with unilateral mMNV eventually develop mMNV in the fellow eye over long-term follow-up. The presence of LCs in the uninvolved fellow eyes was identified as a significant risk factor for mMNV development, supporting the role of mechanical stress in its pathogenesis, and should raise caution during follow-up to enable early detection and timely intervention. Further prospective studies are warranted to validate these findings and to explore preventive strategies in high-risk patients.

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