Prevalence and Phenotypes of Age-Related Macular Degeneration in Eyes With High Myopia

Eleonora Corbelli,[1] Mariacristina Parravano,[2] Riccardo Sacconi,[1,3] David Sarraf,[4,5] Seung-Young Yu,[6] Kiyoung Kim,[6] Vittorio Capuano,[7] Alexandra Miere,[7] Eric Souied,[6] Monica Varano,[2] Antonluca Boninfante,[2] Bora Chae,[4,5] Adriano Carnevali,[8] Lea Querques,[1] Francesco Bandello,[1] and Giuseppe Querques[1]

[1]Department of Ophthalmology, University Vita-Salute, IRCCS Ospedale San Raffaele, Milan, Italy
[2]Fondazione G. B. Bietti-IRCCS, Rome, Italy
[3]Eye Clinic, Department of Neurological, Biomedical and Movement Sciences, University of Verona, Verona, Italy
[4]Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, University of California, Los Angeles, Los Angeles, California, United States
[5]Greater Los Angeles VA Healthcare Center, Los Angeles, California, United States
[6]Department of Ophthalmology, Kyung Hee University, Kyung Hee University Hospital, Seoul, South Korea
[7]Department of Ophthalmology, Hospital Intercommunal de Creteil, University Paris Est Creteil, Creteil, France
[8]Department of Ophthalmology, University of "Magna Graecia", Catanzaro, Italy

PURPOSE. To analyze the frequency and phenotypic variation of AMD in subjects with high myopia (HM), and to describe the clinical course and response to treatment of neovascularization (NV).

METHODS. Patients with HM were identified at five retina tertiary referral centers. Inclusion criteria were myopic patients aged 55 years or more with axial lengths equal or greater than 25.5 mm.

RESULTS. A total of 874 eyes from 442 HM subjects older than 55 years were identified and 104 eyes of 54 patients (72 ± 11 years) were included in the study and followed up for 23.5 ± 19.5 months. The estimated AMD frequency in HM subjects over 55 years was 11.9% (95% confidence interval; 9.8%–14.0%). A total of 34 of 104 eyes were diagnosed with drusen, 22 with reticular pseudodrusen (RPD), 28 with both drusen and RPD, and 20 with geographic atrophy. Neovascularization was detected in 52 eyes (50%), and type 1 was the most frequent form (39 eyes, 75%). Overall, NV was treated with 4.6 ± 2.6 anti-VEGF injections. Eyes with treatment-naïve NV at baseline ($n = 34$) required 3.8 ± 1.5 anti-VEGF injections during the first year of treatment. This exceeded the injection number in the purely myopic population (1.8 to 3.6 injections for the first year).

CONCLUSIONS. This study provides evidence to suggest that older patients with HM are at a significant risk of the dry and neovascular forms of AMD. NV in eyes with HM and AMD required more injections in the first year compared to NV in HM eyes without AMD.

Keywords: age-related macular degeneration, high myopia, drusen, pseudodrusen, geographic atrophy, choroidal neovascularization

A MD is a major cause of visual impairment and blindness in the Western population aged 55 years or older.[1] A combination of systemic and ocular factors may influence AMD onset and progression[2] and further insight into these factors may aid prognosis and risk stratification.

Myopia may have a protective effect on the development and progression of AMD, with a lower prevalence of the disease for each millimeter increase in axial length (AL).[3] In eyes with high myopia (HM), defined as an AL greater than 25.5 mm[4,5] or a refractive error greater than −6 diopters (D; absolute value), decreased scleral rigidity may facilitate diffusion of oxygen and nutrients reducing the risk for AMD development.[6,7] However, there is little information in the literature regarding the prevalence of AMD in older patients with HM and the correlation with associated AMD phenotypes.

The aim of this analysis was to assess the frequency of AMD in eyes with HM and to study AMD subtypes including drusen, reticular pseudodrusen (RPD), geographic atrophy (GA), and neovascularization (NV) occurring in myopic eyes. Although previous studies have compared the NV clinical course in eyes with AMD versus myopic maculopathy,[8,9] this study additionally aimed to analyze NV grade and progression, final anatomic and visual outcomes, and response to anti-VEGF therapy in eyes with AMD and HM.

METHODS

In this retrospective study, subjects were identified from five retina tertiary referral centers (the Medical Retina & Imaging Unit of the Department of Ophthalmology of Vita-Salute San
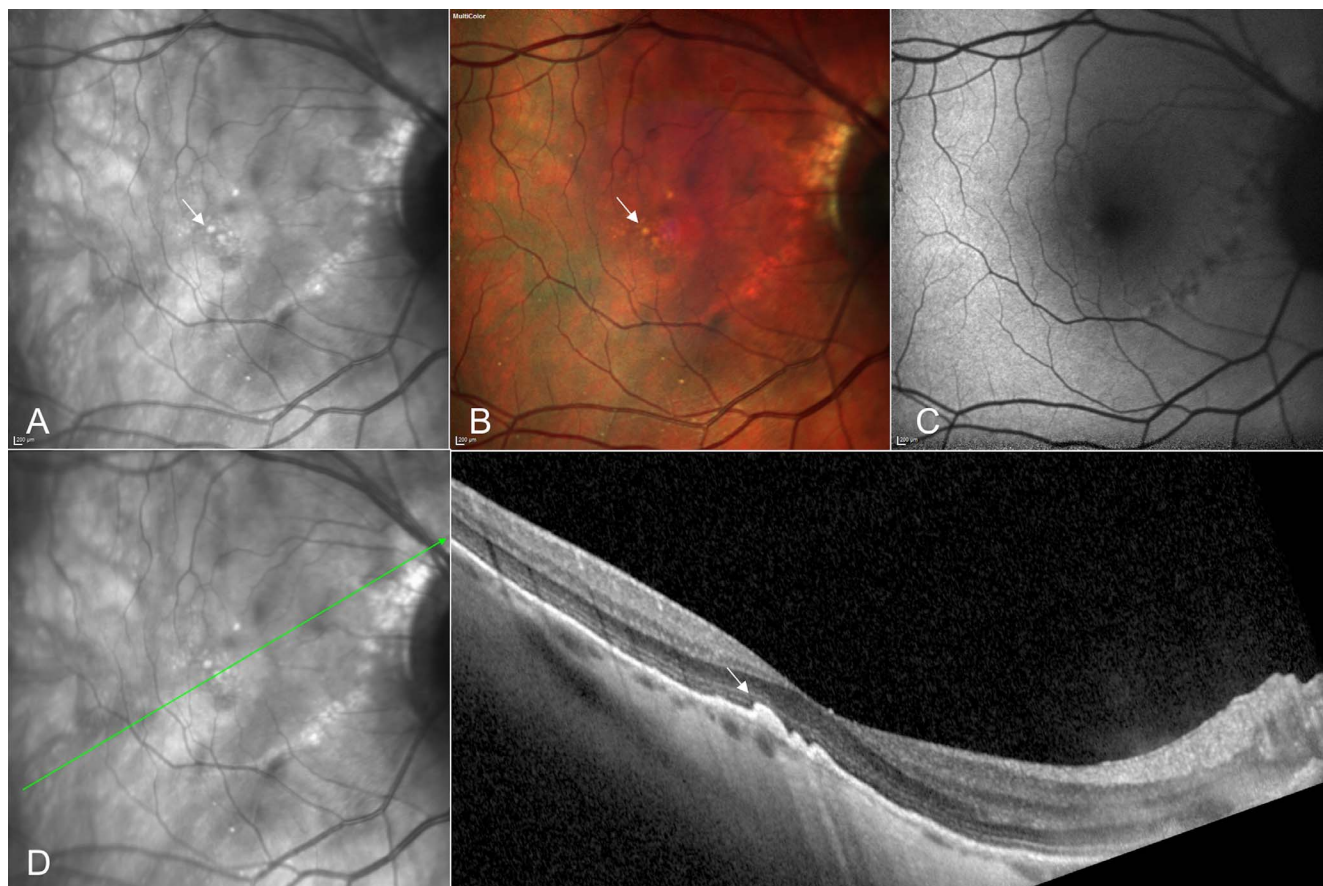
FIGURE 1. Multimodal retinal imaging from the right eye of a 69-year-old woman with HM and AMD illustrating intermediate and large drusen (axial length: 28.11 mm). (**A**) Infrared reflectance, (**B**) MultiColor image, (**C**) fundus autofluorescence. (**D**) IR with registered structural OCT. Note the presence of a myopic fundus associated with a thin choroid and large drusen under the RPE (*arrow*). The AMD overall frequency in highly myopic eyes was 11.9%.

Raffaele University in Milan, Italy; the Department of Ophthalmology of Kyung Hee University Hospital in Seoul, South Korea; the Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, University of California, in Los Angeles, United States; the Department of Ophthalmology of University Paris Est, in Creteil, France; the Department of Ophthalmology of G. B. Bietti Foundation in Rome, Italy). Patients were evaluated between January 2015 and December 2016. The study was conducted in agreement with the tenets of the Declaration of Helsinki for research involving human subjects and was approved by the local institutional review board for all sites.

Inclusion criteria were age equal to or older than 55 years and HM. High myopia was defined as an AL equal to or greater than 25.5 mm, or a refractive error equal to or greater than −6 D of spherical equivalent (SE, meant in absolute value).

We excluded patients with evidence of any retinal disorder (e.g., diabetic retinopathy, retinal vein or artery occlusion, posterior uveitis) other than myopia and AMD and with evidence of significant media opacities (e.g., cataract or corneal opacity) limiting image quality. We also excluded subjects without at least one follow-up examination after the baseline evaluation. The presence of AMD was evaluated according to Spaide's criteria, which encompasses larger disease construct.[10] The new classification integrates RPD, type 3 NV, and polypoidal choroidal vasculopathy (PCV) to the previous clinical spectrum.

All subject charts and imaging were retrospectively reviewed by two expert retinal specialists. The first available visit was considered the "baseline" visit and all the follow-up evaluations were included in the analysis. In any case of discordance between the established diagnosis and the expert-reviewed opinion (e.g., cases of retinal hemorrhage secondary to lacquer cracks), the case was excluded from the study.

As part of standard clinical assessment, all subjects included in the study underwent a complete ophthalmologic evaluation and the following clinical information was collected: past medical and ocular history, Snellen visual acuity (VA) that was converted to logMAR for statistical analysis, and results of slit-lamp biomicroscopy and indirect fundus ophthalmoscopy. Considering the tertiary referral nature of the enrolling centers, multimodal imaging was available for all subjects. Imaging included: infrared reflectance (IR), blue-light fundus autofluorescence (BAF), and structural spectral domain optical coherence tomography (SD-OCT) that were all performed using an HRA + OCT system (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography (FA) and indocyanine green angiography (ICGA) were also performed and the data analyzed when available (e.g., in case of suspect NV). FA and ICGA were performed using an HRA + OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) or a retinal camera (TRC-501X; Topcon, Inc., Tokyo, Japan).

For pseudophakic patients, AL measurements were derived from the biometric calculations, acquired with a biometer (IOLMaster; Carl Zeiss Meditec AG, Jena, Germany).
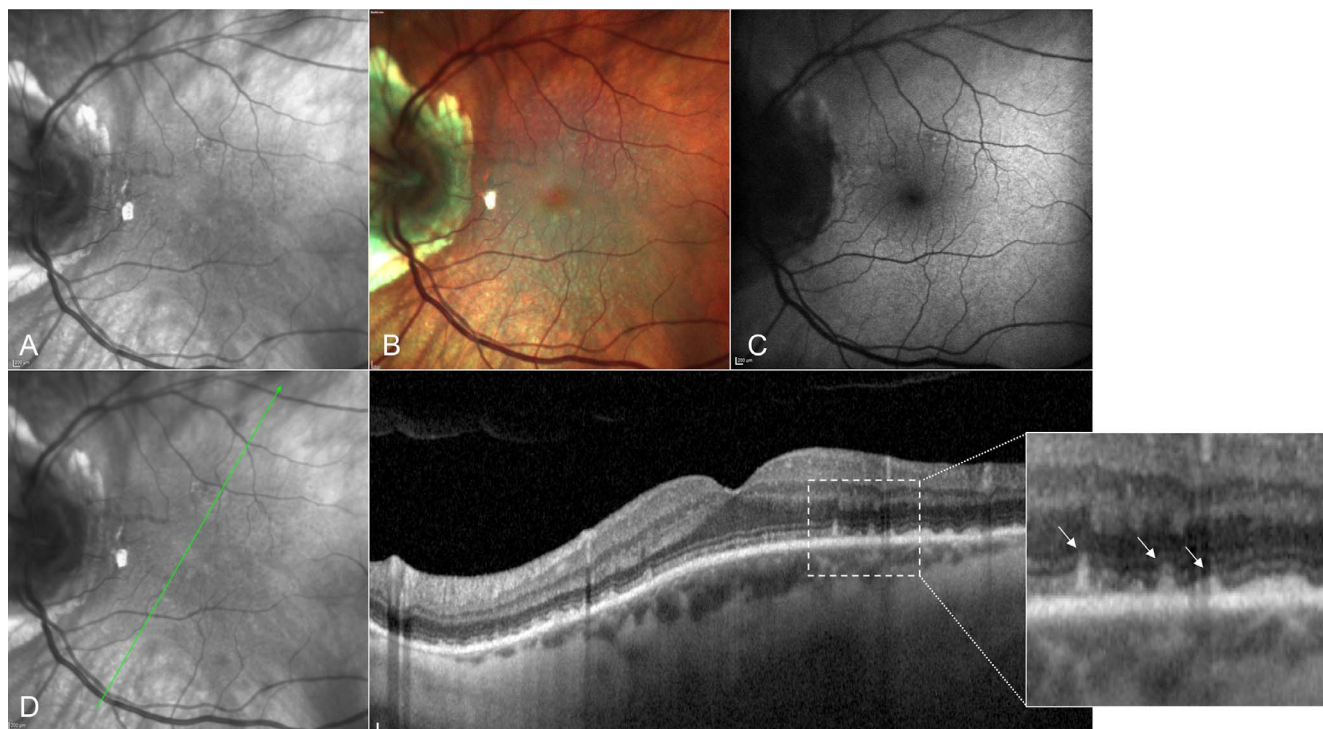
FIGURE 2. Multimodal imaging from the left eye of a 70-year-old man with high myopia and AMD illustrating RPD (axial length: 26.13 mm). (**A**) Infrared reflectance, (**B**) MultiColor image, (**C**) fundus autofluorescence, (**D**) IR with registered structural OCT. Note the presence of a myopic fundus associated with a thin choroid and multiple RPD superior and inferior to the fovea (*arrows*). The frequency of RPD reported in our analysis in dry AMD eyes (19.2% for isolated RPD and an additional 15.4% for sub-RPE drusen and RPD combined).

Central macular thickness (CMT) was assessed in the central 1-mm-diameter circle of ETDRS thickness map using ophthalmic software (Heidelberg Eye Explorer 1.9.11.0; Heidelberg, Germany). Choroidal thickness (ChT) was manually measured as the distance between the Bruch's membrane interface and the sclerochoroidal interface under the fovea.

The different AMD phenotypes before NV development (RPE drusen, RPD, and GA) were also assessed and recorded, and presence of NV was classified based on anatomic localization. Dry AMD is a clinical designation including any RPE drusen, RPD, and/or the advanced stage GA. Wet AMD encompasses any AMD form associated with NV, independently of their type.

According to the Beckman classification,[11] sub-RPE drusen were defined as intermediate if 63-125 μm in diameter and large if ≥125 μm in diameter. The term RPD was used to refer to subretinal drusenoid deposits more prominent in blue light.[12] GA was defined as a well-circumscribed area of at least 175 μm in diameter with baring of the choroidal vessels.[13] According to Gass' classification based on the anatomic criteria,[14] NV was defined as type 1 if located below the RPE, type 2 if located in the subneurosensory compartment, and type 3[15] if an intraretinal proliferation of new vessels was identified.

The details of NV therapy such as the anti-VEGF agent and the number of injections were also assessed and recorded. All the centers adopted common criteria and strategies for anti-VEGF treatment that was administered on a pro re nata (PRN) basis in eyes with FA and OCT evidence of NV. Additional injections were administered in eyes with persistent dye leakage on FA or ICGA and/or intraretinal or subretinal fluid or subretinal hyperreflective material with OCT.

Statistical analyses were performed using statistical software (SPSS Statistics Version 20; IBM Corp., Armonk, New York, USA). All values of descriptive analyses were reported as counts (percentages) for categorical variables, and as average ± standard deviation for quantitative variables. Comparisons of VA, CMT, and ChT between the baseline and the follow-up examination were performed using Student's paired *t*-test or ANOVA *t*-test for repeated measures. In all analyses, values of *P* < 0.05 were considered as statistically significant.

RESULTS

We enrolled a total of 874 eyes of 447 highly myopic subjects older than 55 years (257 females, 190 males; average age 68.3 ± 12.8 years).

A total of 108 eyes of 54 patients (36 females, 18 males) were diagnosed with AMD. Four eyes of four patients were excluded from the analysis because of significant media opacities limiting image quality, hence 104 eyes were analyzed. The average age of the group with AMD was 72 ± 11 years (median 70.5; range 55–93 years).

A total of 30 patients (55.6%) were Caucasian and 24 (44.4%) were Asian. We enrolled 12 patients (22.2%) from the Department of Ophthalmology of University Vita-Salute San Raffaele, 24 patients (44.4%) from the Department of Ophthalmology of Kyung Hee University Hospital, 8 patients (14.8%) from the Bietti Foundation, 8 patients (14.8%) from the Department of Ophthalmology of University Paris Est, and 2 (3.7%) from the Stein Eye Institute.

A total of 24 patients (44.4%) had a history of medically controlled hypertension, 3 patients (5.6%) had a history of type 2-diabetes mellitus, and 3 patients (5.6%) had both disorders.
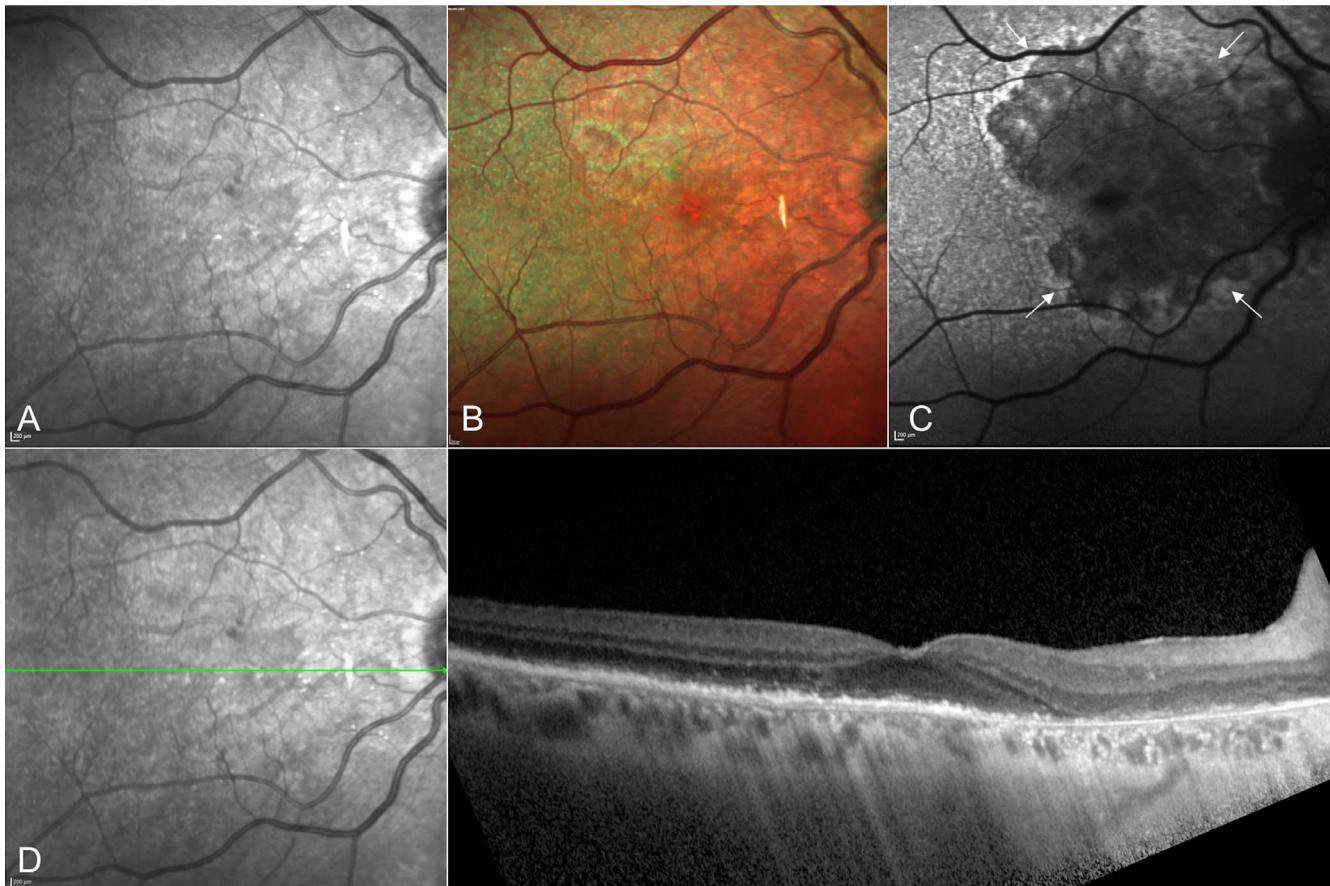
FIGURE 3. Multimodal imaging from the right eye of a 75-year-old woman with HM and advanced form of dry AMD illustrating GA (axial length: 25.91 mm). (**A**) Infrared reflectance, (**B**) MultiColor image, (**C**) fundus autofluorescence, (**D**) IR with registered structural OCT. Note the presence of a myopic fundus associated with GA (*arrows*) in the nasal macula and multiple RPD.

Phenotypes

An estimated eye-specific frequency of AMD of 11.9% (95% CI; 9.8–14.0%) was calculated in highly myopic eyes. A total of 52 eyes (50%) were diagnosed with nonneovascular (dry) AMD, while the remaining 52 (50%) eyes were diagnosed with the neovascular (wet) form.

Within the group with dry AMD, 32 out of 52 eyes (61.5%) displayed early-to-intermediate drusen (Figs. 1, 2) and 20 (38.5%) displayed GA (Fig. 3). Of the early-to-intermediate subtypes, 14 out of 52 eyes (26.9%) showed drusen, 10 showed RPD (19.2%), and 8 (15.4%) showed both.

Within the group with neovascular AMD, 39 out of 52 eyes (75%) exhibited type 1 neovascularization (Fig. 4) while 10 (19.2%) exhibited type 2 NV (Fig. 5), and 3 exhibited (5.8%) type 3 (Fig. 6). No cases of PCV were identified in any of the studied eyes.

Clinical Features

Baseline BCVA in the cohort as a whole was ~20/63 Snellen equivalent (0.48 ± 0.47; median 0.3; range, 0.0–1.6 logMAR). Central macular thickness was 315 ± 91 μm (range, 159–725). Choroidal thickness was 157 ± 43 μm (range, 65–276). As expected, ChT was significantly thinner in patients with RPD versus patients with sub-RPE drusen (179 ± 34 μm vs. 131 ± 31 μm, respectively [$P < 0.001$]).

All 54 patients enrolled were followed for a mean of 23.5 ± 19.5 months (median: 22; range, 4–102). At the end of the follow-up, BCVA was ~20/63 Snellen equivalent (0.48 ± 0.50 logMAR, from 0.48 ± 0.47 logMAR at baseline [$P = 0.949$]) and CMT significantly decreased from 315 ± 91 μm at baseline to 296 ± 78 μm at the end of follow-up ($P = 0.002$).

Axial Length

Fifty-eight eyes (56%) were pseudophakic and 46 (44%) were phakic. Average AL was 27.57 ± 2.04 mm (median: 26.80; range, 25.50–33.80 mm), while average refractive error (spherical equivalent) in the phakic eyes was −7.92 ± 1.88 D (median −7.25; range, −17.00 to −6 D). Eyes with type 2 NV did not show a statistically significant difference in AL versus eyes with type 1 and type 3 NV (mean AL 27.10 ± 0.91 mm vs. 27.64 ± 2.06 mm [$P = 0.420$], respectively).

Treatments

Among the 52 eyes with neovascular AMD, 34 (65.4%) were treatment-naïve. Of the remaining 18 NV cases, 13 out of 52 (25%) were previously treated with anti-VEGF injections (mean of 1.8 ± 0.8 injections per patient), 3 (5.8%) were previously treated with photodynamic therapy (PDT), and 2 (3.8%) were previously treated with both anti-VEGF injections and PDT.

One patient declined any form of therapy while the remaining 51 were treated with a mean of 4.6 ± 2.6 anti-VEGF injections (median 4; range, 1–14) provided on a PRN basis and were followed for a mean of 25.9 ± 21.8 months (median 24; range, 4–102). Of note, 15 out of 51 NVs were
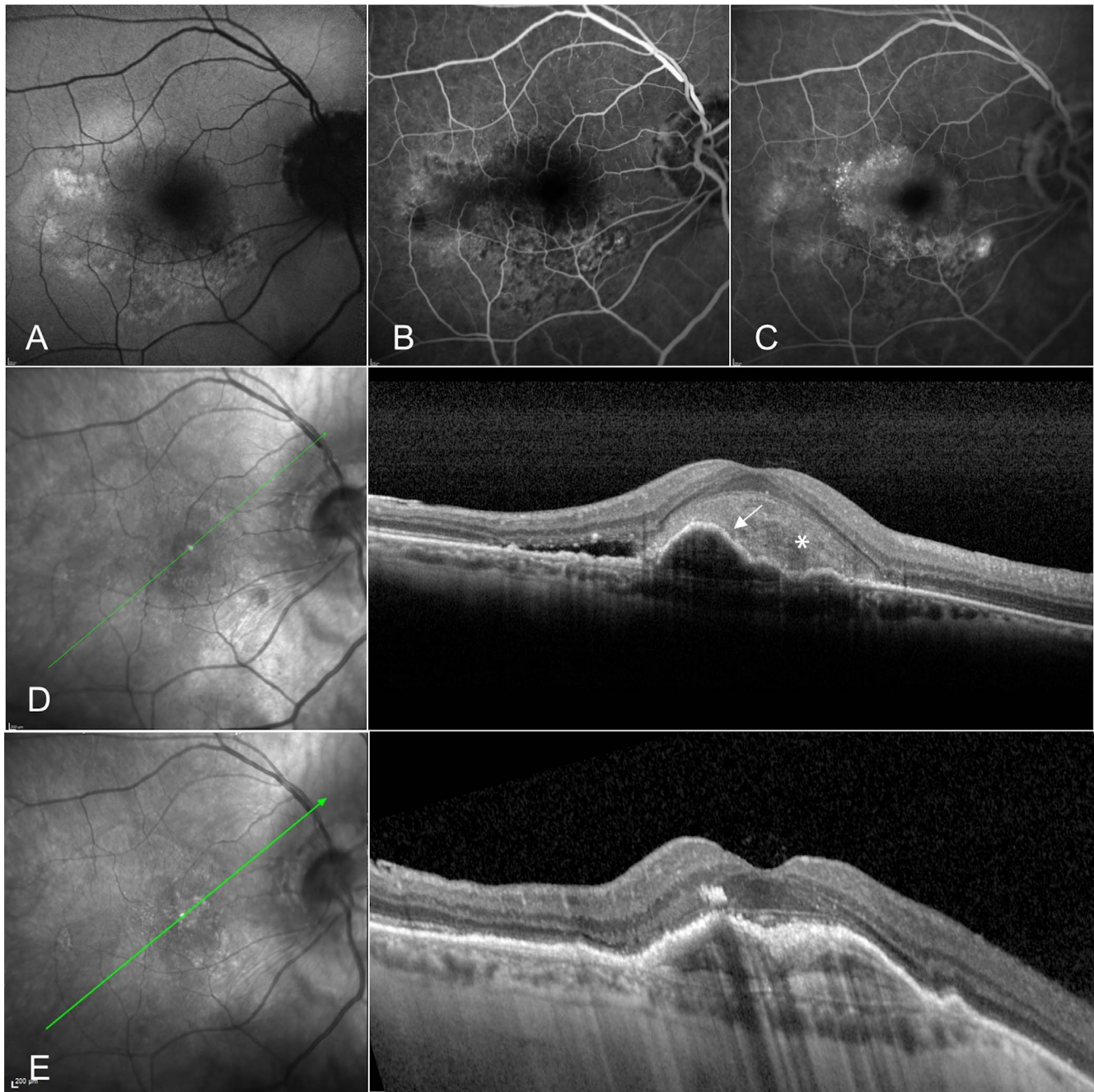
FIGURE 4. Multimodal imaging from the right eye of a 69-year-old man with HM and the neovascular form of AMD characterized illustrating type 1 NV (axial length: 26.29 mm). (**A**) Fundus autofluorescence, (**B**) early, and (**C**) late frames of FA at baseline. (**D**) Infrared reflectance with registered structural OCT at baseline. (**E**) Infrared reflectance with registered structural OCT after treatment. Note the presence of a myopic fundus complicated by type 1 NV inside the edge of the retinal pigment epithelium detachment (PED; *arrow*) and associated with subretinal hyperreflective material (SHRM; *asterisk*) and subretinal fluid with the structural OCT. A corresponding fibrovascular PED with ill-defined stippled hyperfluorescence is noted with the FA. Structural OCT after three anti-VEGF intravitreal injections (**E**) illustrates the resolution of fluid and SHRM.

treated with bevacizumab (1.25 mg/0.05 mL), 26 with ranibizumab (0.5 mg/0.05 mL), and 10 with aflibercept (2.0 mg/0.05 mL) therapy. Of the 34 eyes with treatment-naïve NV at baseline that completed at least 1-year follow-up, a mean of 3.8 ± 1.5 anti-VEGF injections (range, 1–7) were administered during the first year of treatment. No differences in the number of injections were identified between subgroups that received different anti-VEGF agents (data not shown).

DISCUSSION

The purpose of our study was to evaluate the relative frequency of AMD, and the specific features of disease and clinical outcomes, in eyes with HM or high myopia (defined just by spherical equivalent or axial length parameters) in patients aged over 55 years.

We found the AMD overall frequency in highly myopic eyes was 11.9% (Figs. 1–6), comparable with the data reported in
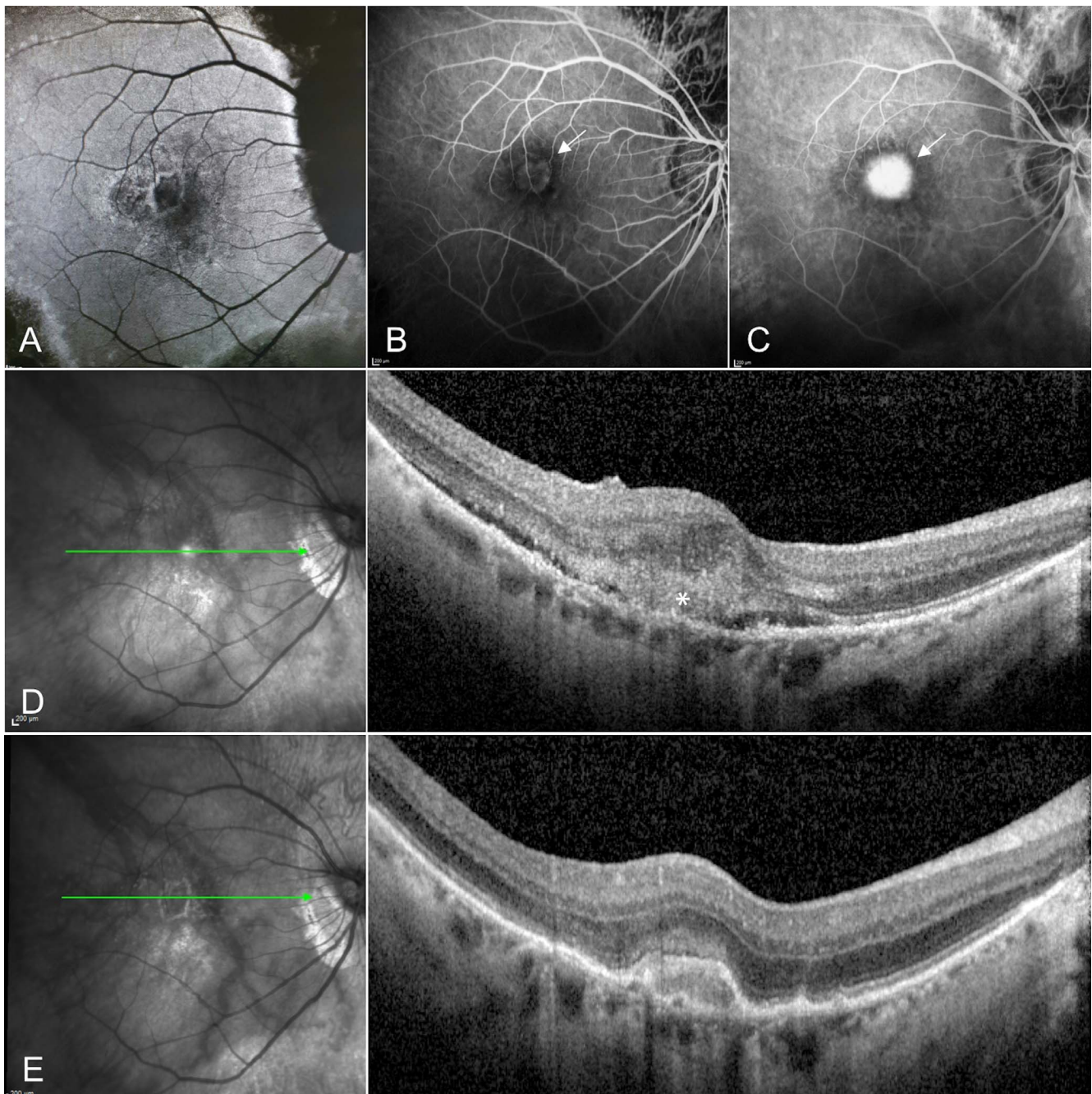
FIGURE 5. Multimodal imaging from the right eye of a 70-year-old man with HM and the exudative form of AMD illustrating type 2 NV (axial length: 27.02 mm). (**A**) Fundus autofluorescence, (**B**) early, and (**C**) late frames of FA at baseline. (**D**) Infrared reflectance with registered structural OCT at baseline. (**E**) Infrared reflectance with registered structural OCT after treatment. Note the presence of a myopic fundus and associated NV (*asterisk*) and subretinal fluid with the structural OCT corresponding to well-defined hyperfluorescent subfoveal lesion with leakage with FA (*arrow*). Structural OCT after 2 anti-VEGF intravitreal injections (**E**) illustrates the resolution of fluid and subretinal hyperreflective material.

the general population affected by AMD.[16-18] This result is in contrast to the outcomes of previous studies which have reported that HM eyes were less likely to manifest any form of AMD, suggesting a potential protective role.[3-7] This protective effect has been attributed to reduced ultraviolet exposure in sunlight, a known AMD risk factor, due to spectacle use[19] or to lower ocular scleral rigidity in HM subjects that may facilitate the diffusion of oxygen and nutrients to the macula, protecting eyes against AMD.[7] The data collection from tertiary referral centers might justify this disparity, ensuing to an overestima-

tion of AMD frequency in HM eyes. Hence our results may not be completely representative of the general population.

There is a dearth of information in the literature regarding the description and prevalence of various AMD phenotypes in highly myopic eyes. The frequency of RPD reported in our analysis in dry AMD eyes (19.2% for isolated RPD and an additional 15.4% for sub-RPE drusen and RPD combined; Fig. 2) seems higher than that reported for patients with AMD.[20,21] This finding may be explained by the fact that our myopic cohort exhibited a reduced choroidal thickness. It is indeed well documented that RPD are associated with a thinner
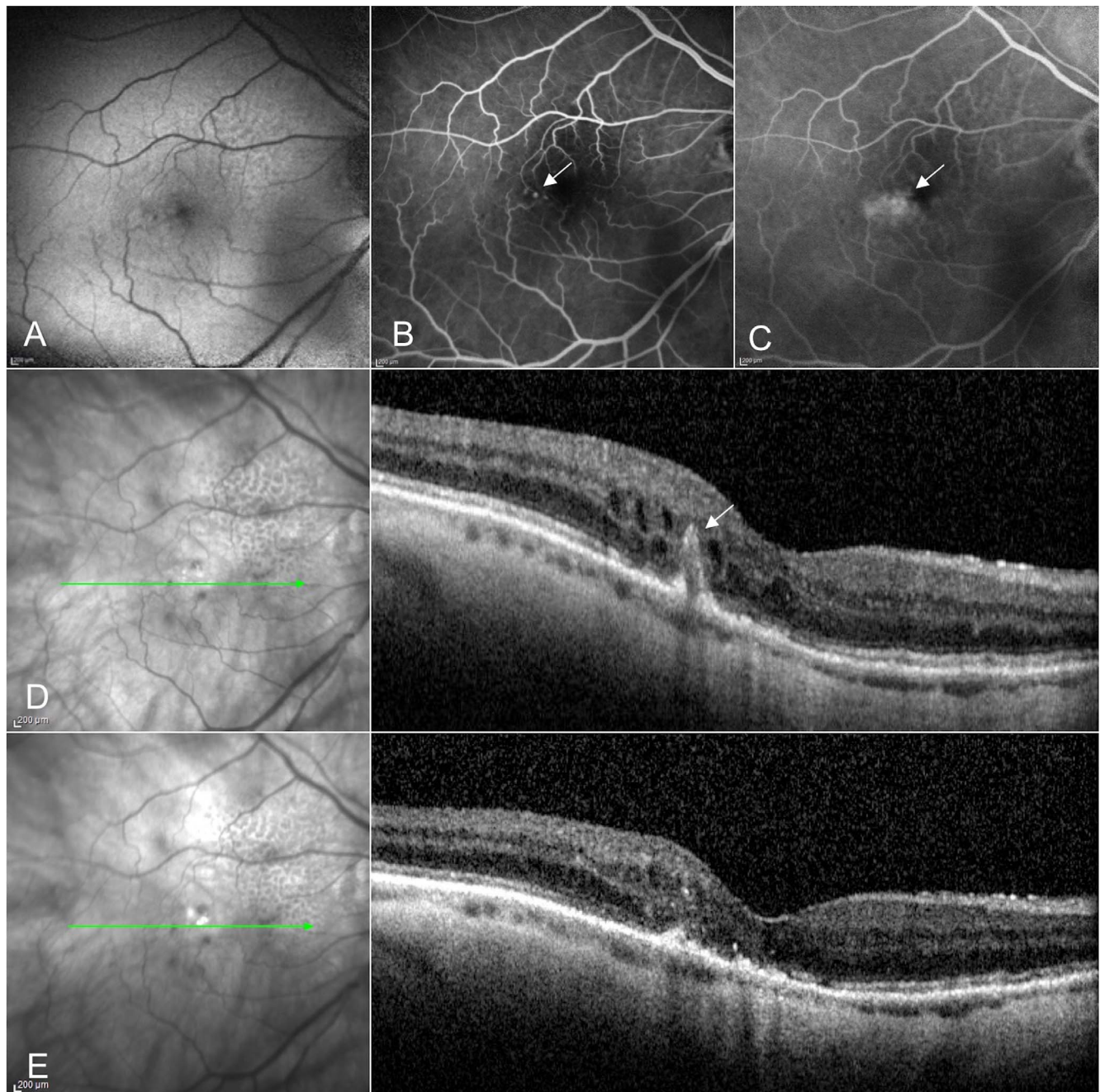
FIGURE 6. Multimodal imaging from the right eye of an 89-year-old man with HM and the exudative form of AMD illustrating type 3 NV (axial length: 26.71 mm). (**A**) Fundus autofluorescence, (**B**) early, and (**C**) late frames of FA at baseline. (**D**) Infrared reflectance with registered structural OCT at baseline. (**E**) Infrared reflectance with registered structural OCT after treatment. Note the presence of a myopic fundus and an hyperfluorescent spot with leakage in the late phase of the FA (*arrow*) that colocalizes with the intraretinal hyperreflective focus with structural OCT (*arrow*). Structural OCT after 2 anti-VEGF intravitreal injections (**E**) illustrates the resolution of fluid.

choroid,[10–22] as proposed by Querques et al.,[23] who stated that RPD may be the result of choroidal atrophy and ischemia leading to photoreceptor outer segment disruption and accumulation above the RPE.

Neovascular AMD was detected in half of the enrolled eyes (50%) in this study, of which type 1 NV was the most common subtype encountered (75%). This finding contradicts numerous published reports of a higher incidence of type 2 NV in HM eyes.[24–26] Structural OCT studies have noted that myopic NV typically displays a hyperreflective dome-shaped lesion with fuzzy borders above the RPE (i.e., type 2 NV) and minimal subretinal or intraretinal fluid in the majority of cases and associated lacquer cracks or RPE atrophy.[27] Interestingly, in older subjects, myopic NV has been characterized by a larger size and poorer outcomes.[27] The key factor explaining the development of type 2 NV in myopia versus type 1 NV in AMD is age, as originally described by Gass.[28] He noted that the RPE-Bruch complex is much more adherent in younger patients leading to the development of type 2 NV in eyes with disorders affecting a younger population (e.g., myopia, punctate inner

choroidopathy, choroidal rupture, idiopathic). In older patients with AMD, the RPE-Bruch complex is less adherent predisposing to RPE detachment associated with type 1 NV. This may be further facilitated by the presence of drusen (and basal linear and basal laminar deposits), which may further promote a cleavage plane between the RPE and Bruch's membrane layers. Our myopic cohort was significantly older, which may explain the greater incidence of type 1 NV.

The different mechanisms involved in the development and growth of NV secondary to AMD and pathologic myopia may also play a role. Myopic NV (type 2) is promoted by upregulated production of VEGF[29] due to altered choroidal perfusion and RPE-Bruch's membrane-choriocapillaris degenerative changes. On the other hand, in neovascular AMD, the most typical pattern is type 1 NV, because the presence of drusen and accumulated waste products exacerbate choroidal blood flow reduction and oxidative stress[30,31] leading to stimulation of VEGF expression mainly beneath the RPE. In our series, both pathologic mechanisms may be involved, but the NV phenotype of our older myopic cohort was more similar to AMD patients. Therefore, it may be speculated that the occurrence of type 1 NV in eyes with HM and AMD supports an AMD-related pathogenesis.

We were not able to identify any clinical or multimodal imaging features of choroidal neovascularization that can indicate the underlying cause (AMD versus HM) of the NV. However, the presence of a very thin choroid (i.e., leptochoroid)[32] associated with signs of myopic maculopathy, such as lacquer cracks, may provide clues to the diagnosis of myopic NV and may indicate the need for axial length measurement. Myopic NV even in older patients, as in our study, does not require as aggressive a regimen of anti-VEGF therapy as in the typical AMD population.[33,34]

Anti-VEGF therapy is the first-line treatment for NV in AMD and myopic maculopathy. However, in our study, NV in eyes with concomitant AMD and HM showed a different clinical course and response to treatment compared to NV associated with typical AMD, as previously reported in the literature.[33,34] In our population, more anti-VEGF intravitreal injections were needed to restore functional and anatomic parameters than that reported in the purely myopic population[35–38] (3.8 injections in our AMD/myopia population versus 1.8–3.6 injections in the purely myopic population using a PRN protocol in the first year of treatment).[28–31] However, 3.8 represents a reduced number of injections needed to optimally treat NV in AMD (4.3–6.9 injections in the first year of PRN treatment has been reported).[33,34] Therefore, neovascular AMD in HM may have an intermediate severity pattern between pure myopic maculopathy and pure AMD. Either way, our analysis emphasized the need for vigilant monitoring of eyes with AMD and HM, and frequent anti-VEGF therapy. It is unclear whether the lower injection number in our study may be due to less severe AMD forms affecting the HM group.

Potential limitations of our study should be noted. We acknowledge the small sample size, due to the retrospective design and the strict inclusion and exclusion criteria. Our investigation was not a true population-based study. Therefore, larger and longer prospective studies are needed to provide more robust analysis and validation of the results of our report, especially the frequency (11.9%) of AMD in an older population with high myopia. Furthermore, our data was obtained from tertiary referral centers. This selection bias may have skewed our findings toward a more severe variant of the disease, and, moreover, may have led us to an overestimation of AMD frequency in HM eyes. Eventually, the triggering cause (AMD versus HM) in charge for the NV development was not demonstrable based on clinical or multimodal imaging features only.

In conclusion, this study has provided evidence that HM eyes are at a significant risk of AMD and that high myopia may not be protective. In addition, our report illustrated that the most frequent late AMD phenotype was the neovascular form complicated by type 1 NV, requiring sustained anti-VEGF therapy. These findings may support ophthalmologists in their assessment and management of HM patients with coincident AMD, which is especially important given the rising trend in incidence and prevalence of these two diseases that represent important public health concerns.

Acknowledgments

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