Title: Progression of Myopic Maculopathy in a Caucasian Cohort of Highly Myopic Patients with 12 Years of Follow-Up: A Multistate Analysis

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ABSTRACT:

PURPOSE: To determine the probability of progression of myopic maculopathy according to age.

METHODS: Longitudinal observational study of single-center retrospective cohort of Caucasian patients formed by 212 consecutive adults with High Myopia. Main outcome measures were age, sex, family history, visual acuity, refractive error, follow-up time, peripapillary atrophy, and presence of staphyloma. The macular status was assessed according to the Meta-Analysis of Pathologic Myopia Study Group. Subgroups with or without pathologic myopia were compared. The progression rate was calculated based on 1,000 eyes/year. Multistate models were fitted to identify the predictive factors and to calculate the most probable age of progression onset using the Aalen-Johansen estimator.

RESULTS: We studied 220 eyes of 122 Caucasian patients. Mean age was 48.18±14.1, mean follow-up 12.73±5.81 years. Ninety-six (44%) eyes worsened by an average 0.3 logMAR unit during follow-up. The following ages have been identified as key in progression. The probability of progressing from category 1 was >0.6 after age 70 and >0.7 if after age 45 if choroidal neovascularization (CNV) developed. From category 2 it was 0.7 over 70 years of age, but with lacquer cracks it was 0.75 after 32 years, and if CNV developed it was 0.7 after 52 years. The probability of progressing from category 3 exceeded 0.75 from age 55 if CNV was present.

CONCLUSION: This study provides new information contributing to predict the probability of progression of myopic maculopathy throughout life, which could be important for its prevention and management.

Key Words: High Myopia, Pathologic Myopia, Myopic Maculopathy, Choroidal neovascularization, lacquer cracks, Multistate Models, Risk Factors of Progression.

DECLARATIONS

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INTRODUCTION

High Myopia is defined as a negative refractive error higher than -6 to -8 diopters (D) or an axial length over 26 to 26.5 mm [1]. These eyes are most at risk of developing macular changes due to an excessive axial elongation that induces the posterior staphyloma formation [2]. When macular changes or posterior staphyloma appear, we can speak about Pathologic Myopia, which is one of the most significant causes of blindness worldwide [3]. Thus, various lesions, such as lacquer cracks (LCs), choroidal neovascularization (CNV) leading to Fuchs' spots, and myopic chorioretinal thinning or atrophy, may appear in Pathologic Myopia on the posterior pole related to staphylomas [4]. The Meta-Analysis for Pathologic Myopia (META-PM) Study Group [5] proposed a definition of myopic maculopathy and a classification system based in retinographies by which the fundus appearance was graded as category 0 with no myopic retinal lesions; category 1, tessellated fundus; category 2, diffuse chorioretinal atrophy; category 3, patchy chorioretinal atrophy; and category 4, macular atrophy. The authors added three "plus signs," i.e., LCs (plus sign 1) and CNV (plus sign 2) leading to Fuchs' spots (plus sign 3), and considered the presence of posterior staphyloma as an important sign of Pathologic Myopia [5]. Fang et al. later revised that classification and defined of having Pathologic Myopia those eyes presenting myopic maculopathy catalogued as $\geq$ category 2 and/or the presence of any plus sign [6]. They also modified slightly the META-PM classification considering CNV, Fuchs' spots and CNV related macular atrophy altogether [6].

The prevalence of myopia is high in Spain and one of the highest in Europe and only higher in Asian populations [7]. This prevalence is increasing, and therefore myopia-related complications derived from it, with implications for planning health services to prevent and treat them [8,9].

Risk and protective factors for progression in myopic maculopathy have been

published [6,10], and reports have described the progression rates and patterns of myopic maculopathy over time, although they were determined within distinct racial settings or using different classifications [6,10-13]. Varying the definition of myopia may affect the estimates of its prevalence and associated risk factors[14].

In clinical practice, most ophthalmologists would be interested in predicting in what extent, a precise patient with myopia may evolve based on age and when visual impairment may appear during his/her life which could be useful in prevention and management. Multistate models are useful statistical tools that allow the establishment of the probability of changes occurring over time during a disease course such as high myopia. Through these models, a patient can be classified into one of a finite number of stages (in this case, five categories and three plus signs) at any time during follow-up. A transition would represent a stage change in the disease process. The times of transition correspond to the times (ages in the current study) when it is more probable that changes will occur [15]. The objective of this study was to obtain new information on the progression of myopic maculopathy using a classification of consensus and multistate models to predict the progression according to age in a Caucasian population by identifying risk and protective factors. In addition, the rate of progression of myopic maculopathy/1,000 eyes/year is calculated for this sample, which allows to eliminate the effect of the different follow-up times of each patient.

METHODS

This longitudinal observational study of single-center retrospective cohort followed the tenets of the Helsinki Declaration of 1964 (last amendment, 2013); the Clinical Research Ethics Committee of the Valladolid East Health Area approved the study.

The study was performed at the Instituto Universitario de Oftalmobiología Aplicada Retina Unit, University of Valladolid, Spain. A database that included 212 consecutive Caucasian patients with refractive errors of −6 diopters (D) or higher examined at least once between August 2004 and September 2008 was reviewed. Eyes that required vitrectomy and those without retinographies at least 5 years apart or poor retinography quality were excluded. Other exclusion criteria were incomplete data, ocular hypertension, retinal or choroidal disease that altered the fundus.

Variables

The variables studied included sex, family history of myopia, follow-up time, and presence of peripapillary atrophy and staphyloma. The refractive error was measured in spherical equivalent (D) at baseline and the final visits. The best-corrected visual acuity (BCVA) was recorded using Early Treatment of Diabetic Retinopathy Study optotypes (Lighthouse, Long Island, NY) using the logarithm of the minimum angle of resolution (logMAR) scale.

Fundus photographs (50^{o}) were obtained either with the TRC 50DX Retinograph (TOPCON Europe Medical BV, Rotterdam, the Netherlands) or with spectral-domain optical coherence tomography (SD-OCT) model 3D OCT 2000 (TOPCON Europe Medical B.V.). Two patients had old good-quality polaroid retinographies that permitted extension of the follow-up period. All fundus photographs were examined by two ophtalmologist (MB and RMC) independently and in case of disagreement a panel decision was made. The retinographies were graded according to the modified META-PM Study Group international classification [5,6]. When a category change was observed or a plus sign developed along successive visits the ages at which the change was observed were recorded. The age of appearance of plus signs was also gathered i.e., LCs (plus sign 1) and CNV (plus sign 2) leading to Fuchs' spots (plus sign 3), although the two latter were

analyzed together calling them CNV, considering that the latter results from the former [6,16]. According to Fang et al., patients were subdivided into two subgroups, those with Pathologic Myopia at the first visit (eyes with myopic maculopathy category category ≥ 2 and/or the presence of any plus sign), and those without Pathologic Myopia (category 0 or 1, without any plus sign) [6]. Myopic maculopathy progression was defined as an evolution to a superior category and/or the appearance of a plus sign.

Statistical Analysis

We described the distribution of the main parameters for the total sample and for both subgroups (with/without Pathologic Myopia) by calculating the means and standard deviations of the continuous quantitative variables and calculating the frequencies and percentages for the categorical ones. The unit of study was each eye according to the design of other similar studies that were used to compare our results [6,12,13].

For the comparison between subgroups, the Student t-test was used for quantitative variables. The assumption of normality was checked by Kolmogorov-Smirnov test and homogeneity of variance by the Brown-Forsythe test, a modification of Levene's test. When these assumptions were invalid, the Mann-Whitney U-test or the Welch test was applied. Relationships between the subgroup and qualitative variables were evaluated by the chi-square test or Fisher's exact test with small expected cell counts.

The rate of progression is expressed as a /1,000 eyes/year. This was calculated as the ratio of the number of events meaning progression (change of category or appearance of any plus sign) divided by total follow-up person time as recommended by Jabs to minimize the effect of different follow-up time of each patient [17].

Multistate models were applied to the total sample. The age at which myopic maculopathy progressed toward a more advanced disease stage allowed calculation of the

probability of evolution according to age. Because it is impossible to fit the model considering both the categories and the plus signs simultaneously, two models were designed: 1) the evolution to a more severe category in which each eye was classified as category 0 to 4 at the beginning of the study and the age at which the disease would probably evolve to superior category during follow-up was estimated; and 2) within each category another model fitted with any preexisting plus sign or plus sign development. Multistate modeling was performed by non-parametric hazards in the framework of the Cox model [18]. We assumed that the process is Markovian, implying that the time course can be described by assigning every patient to a distinct stage at any defined time and that the transition intensities only depend on the history of the process through the present stage. Transition probabilities, representing the risk of a transition occurring at a given time, were estimated using the Aalen-Johansen estimator [19]. Sex, family history of myopia, BCVA, and refractive error at the first visit; presence of staphyloma and of peripapillary atrophy were incorporated as covariates in the multistate models through transition intensities to explain the differences among individuals in their disease processes and predict each eye's risk of the event of interest. Modeling associations between covariates and transitions were based on Cox's proportional hazards model [18] for each of the transition hazards separately. The Schoenfeld residuals test [20] was used to check the assumption of proportional risks within every transition.

$P < 0.05$ was considered to be significant. Statistical analyses were performed with R Statistical Software Version 3.5.2 (R Foundation for Statistical Computing 12/20/18, Vienna, Austria). Analyses of the multistate models were performed with the R package mstate`2+1 .

RESULTS

From a database of 212 patients, 32 patients were non-evaluable due to lack of fundus photography, and 180 were evaluable (290 eyes). Of these, 70 eyes were excluded, due to lack of follow-up (n = 25), refractive defect no ≥ -6D (n = 25), retinal detachment (n = 10), punctate inner choroidopathy (n = 4), glaucoma (n = 2), ocular trauma (n=2) and 1 eye, respectively, for macular hole and prostheses. Thus, 220 eyes of 122 patients (85 women, 69.67%; 37 men, 30.33%) were included in the study. In 98 patients, both eyes were included.

The mean follow-up was 12.73 ± 5.81 years (range, 5-47). A family history of high myopia was positive in 129 (61.7%) patients. Peripapillary atrophy was present in 204 (92.7%) eyes; staphyloma was present in 204 (92.7%) eyes. The mean ages at development of LCs were 47.25±13.11 years (n=44), and CNV, 53.97+16.47 years (n=48). The time to second eye involvement was 5.82±10.4 years if the CNV was bilateral (n=17). Ninety-six (44%) of 218 eyes worsened by an average of 0.3 logMAR unit (range, 0.1-2.6) during follow-up (2 missing). Table 1 shows the baseline and final characteristics.

Differences in progression between eyes with/without Pathologic Myopia

Table 2 shows the characteristics of the total sample, patients with myopic maculopathy ≥ category 2 (Pathologic Myopia) and those with myopic maculopathy category 0 or 1 (without Pathologic Myopia). The percentage of eyes that progressed during follow-up was 69.1% (152 of 220).

The progression rate in eyes included in category 0 at their first visit was 573.43/1,000 eyes/year; starting from category 1, the progression rate was 84.68 and increased to 784.86/1,000 eyes/year if a plus sign developed. Table 3 shows the baseline characteristics and progression rates of different categories of eyes with Pathologic Myopia.

Peripapillary atrophy and the initial refractive error were significantly higher in eyes without Pathologic Myopia at baseline that progressed (*P*=0.0171 and *P*=0.0282, respectively). The proportion of women was significantly (*P*=0.0109) higher among the patients in which myopic maculopathy progressed.

Table 4 shows the comparison of progression in the current study and some Asian studies.

Multistate Models

To perform the multistate analysis, we considered the total eyes in each category at different times during the follow-up. Figure 1 shows the data measured in our sample

Figure 2 shows the probability of transitioning between different categories. The distance between adjacent curves represents the probability of being in a particular category at a given age. For example, Figure 2A shows that the probability of progressing to category 1 at 35 to 40 years was 0.15-0.2, similar to the probability of progressing to category 2 between 45 and 65 years. The probability of evolution to category 3 was <0.2 until the age of 50 and around 0.4 between 65 and 75 years. The probability of developing category 4 was nearly 0 until 55 years and increased from there with age. Figure 2B shows that starting at category 1 the probability to progress to category 2 was 0.4 between 45 and 55 years, to category 3 0.2 until age 50, and 0.4 between 63 and 74 years; and the probability of progressing to category 4 exceeded 0.5 from age 75. Figure 2C shows that the probability of evolving from category 2 to superior category was 0 until 25 years, and the probability of progressing to category 4 was 0 until 40 years. The probability of progressing to category 3 was about 0.5 at 25 to 30 years and >0.5 from 65 years. Figure 2D shows that **s**tarting in category 3, the probability of progressing to category 4 was 0 until the age of 40 and >0.7 from 70 years.

From category 1, the risk of progressing increased in women (RR=2.054; 95% confidence interval [CI], 1.348-3.131; *P*=0.0008). Positive family history was associated with the risk of progressing to category 3 (RR=1.913; 95% CI, 1.913-1.026; *P*=0.0412)

With worsening by one unit, the initial logMAR BCVA increased the risk of developing category 4 (RR=5.8; 95% CI, 2.603-12.923; *P*<0.0001). With decreasing by one unit, the myopic initial refractive error decreased the risk of progressing to category 2 (RR=0.929; 95% CI, 0.889-0.97; *P*=0.0009), category 3 (RR=0.892; 95% CI, 0.851-0.935; *P*<0.0001), or category 4 (RR=0.892; 95% CI, 0.816-0.975; *P*=0.0121).

Figure 3 shows the probabilities of transitioning both to a superior category and developing a plus sign, when starting without a plus sign.

Figure 4 shows the probabilities of transitioning with any coexisting plus sign at baseline. The multistate models of the transitions of eyes starting at category 4 could not be performed because only three of 47 eyes progressed to development of CNV.

In these graphs, the ages at which each change is more likely to occur can be calculated based on the starting stage and the appearance of plus lesions. Some other important results are highlighted below.

From category 1, the probability of developing LCs was 0.1 at 47 to 48 years; the probability of progressing to CNV was 0.1 at 53 to 57 years and 0.16 at 86 to 87 years; and the probability of progressing to superior category was >0.6 over 70 years (Figure 3.A). Starting with LCs, the probability of developing CNV was >0.25 between 32 to 40 years, and the probability of developing superior category was >0.6 from age 60 (Figure 4.A). Starting the follow-up with CNV, the probability of developing superior category was >0.7 from 45 years (Figure 4.B). With a decrease of one unit, the myopic initial refractive error decreased the risk of progressing from category 1 to LCs (RR=0.803; 95% CI, 0.733-0.88; *P*<0.0001) and to superior category (RR=0.78; 95% CI, 0.704-0.865; *P*<0.0001).

From category 2, we found a probability of 0.1 for developing LCs at 45 years and CNV between 49 to 50 years. The probability of progressing to superior category was 0.7 after 70 years (Figure 3.B), but if LCs were present the risk was 0.75 after 32 years (Figure 4.C). With CNV the probability of progressing was >0,7 from 52 years (Figure 4.D).

From category 3, the probability of progressing to CNV was 0.1 between 49 to 55 years and 0.2 between 70 to 75 years. The probability of progressing to superior category was 0.1 from 54 years and 0.5 after 75 years (Figure 3.C). Patients with CNV had a probability >0.75 of advancing to superior category from 55 years (Figure 4.F). Female gender increased the risk of evolving to superior category (RR=4.284; 95% CI, 1.245-14.735; *P*=0.021). With an increase of one unit, the logMAR baseline BCVA increased the risk of developing CNV (RR=2.15; 95% CI, 1.18-3.917; *P*=0.0124); and with a decrease of one unit, the myopic initial refractive error is protective from developing superior category (RR=0.858; 95% CI, 0.754-0.977; *P*=0.0211).

Finally Figure 5 shows an example of progression.

DISCUSSION

This study is noteworthy for public health considerations, because it establishes surveillance measures for patients who are at ages at risk for development of treatable complications such as CNV. Using consensus classifications is advisable in high myopia studies because small changes in its definitions may significantly affect the results [14]. The classification we used is a consensus and has the advantages of having a high inter- and intra-observer reproducibility that allows comparison of our series with some Asian studies [6]. Ruiz-Medrano et al. recently proposed a new more comprehensive classification system for Myopic Maculopathy based on atrophy, traction, and neovascularization [22]. This system is similar for the atrophic changes but includes

myopic tractional maculopathy. Nevertheless, it was published during the time that the current study was ongoing, and not all patients in our series underwent SD-OCT at baseline.

The current study included a high proportion of female patients, which agrees with published data [11,23-25]. Present series have a high prevalence of staphyloma (92.7%) compared with other series (23%-55%), although Ohno-Matsui et al. and Chang et al. did not find ethnicity differences between an Asian and Spanish cohort using wide-field images [9,26,27]. The high rate of staphyloma found may be explained by the fact that patients with normal fundi may have lacked retinographies and thus were not included in the study. In addition, peripapillary atrophy occurred in more than 90% of eyes, similar to the 81.2% reported by Chang et al. who described it as the most frequent finding in eyes with high myopia. Nevertheless, those authors reported different proportion of staphyloma or peripapillary atrophy between distinct Asian populations [27]. These changes also have a relationship with higher axial length [28], and in eyes with a refractive error of at least -10 D something also stablished in our study [10]. Finally, we found a positive family history in most patients, as already reported [29].

The BCVA worsens with disease progression and therefore with increasing age [11,30,31]. The current series is not a natural history study as that of Hayashi et al. [11], and the visual outcomes may have been affected by the appearance of anti-vascular endothelial growth factor treatments during the follow-up of our cohort, although worsening occurs anyway. This made it difficult to compare our visual outcomes with other reported series.

The proportion of eyes progressing to Myopic Maculopathy was higher in our series (69.1%) than in those of Fang et al. (58.6%), Hayashi et al. (40.6%), Yan et al. (35.5%) and Vongphanit et al. (17.4%) possibly because of different mean ages, distinctive refractive

errors, or different follow-up periods [6,11,12,23]. The higher number of patients with staphyloma may have contributed too. The age-adjusted prevalence of Myopic Maculopathy (especially for categories categories 2 and 3) has increased significantly over the past 12 years, which also may explain our higher figure [32].

The rate of progression/1,000 eyes/year was higher in the series of Fang et al., who reported higher progression rates in eyes with Myopic Maculopathy than in eyes without it, in contrast to our findings. Other differences may be because they included children, patients with a refractive error of -8 D, and/or because the average follow-up was 18 years with a minimum of 10 years, which was longer than ours [6].

The differences between the subgroups with and without Pathologic Myopia were the expected ones. We found higher percentages of progression in each category compared to Asian series [23,25,33]. We found a high probability of progression to a superior category in young patients, which may be due to the development of a plus sign because, although the proportion of eyes with a plus sign was similar to that found in other series, it appeared in younger patients in our series. Besides, LCs were found in 10% at baseline in our series, which is similar to the 15.7% reported by Ohno-Matsui et al. [34], or the 9.5% found by Choudhury et al. [13]. Like the current series, the Asian series found that LCs tended to appear in lower categories and myopic CNV in more advanced categories and thus older patients. In addition, 21.9% of our patients had CNV at baseline, which increased to 35.5% at the last visit, providing an increment of 13.6% that is similar to the 10.2% observed by Ohno Matsui et al. with a 10-year follow-up. Those authors also identified CNV more frequently in category 3 (20%), when there were LCs (29.4%) or preexisting CNV in the fellow eye (34.8%), and less frequently in eyes with category 2 (3.7%) [34]. In contrast, we found CNV occurring in more incipient categories (14.7% from category 1, 17.6% from category 2, 33% from category 3, and 16.27% in eyes that had LCs) [6,11,12,34].

Multistate models seem to be a robust statistical method with the advantage of determining the risk at a given age. In contrast, standard survival analyses using Kaplan–Meier curves and Cox regression analyses for the all-events hazard do not allow calculation of risk factors [15]. A lower myopic initial refractive error was a protective factor and the identified risk factors of progression in our study were: female gender, family history and worse initial BCVA, similar to those reported by Fang et al. (female gender, advanced age, greater axial length, and development of peripapillary atrophy) [6], Yan et al. (longer axial length, older age, presence of staphyloma, and female gender) [12], and Liu et al. (increased age, worse BCVA, deeper anterior chamber, larger optic disc, less age-related macular degeneration, and higher prevalence of open-angle glaucoma) [10].

The retrospective design of the current study was a limitation because it did not permit analysis of eyes without retinographies. Nevertheless, the approach through multistate models provides a prospective nature to the study, since the series is analyzed from the baseline to the final state, which partly avoids the negative effect of the retrospective nature of data acquisition. Besides, the current study is a relatively large series with a long follow-up, except for the subgroup starting in category 4 but this is because only older patients with a very high refractive error end-up in that state which decreases the number of possible subjects who comply. In any case the study allows plausible characterization of progression patterns and prediction of the sequence of changes in the macular status attributable to aging in high myopia thanks to a new statistical approach. We also did not include patients younger than 18, so predictions are not available for that age group, but usually at that age Myopic Maculopathy is not yet a clinical problem.

In summary, our results add data to the knowledge of this growing public health challenge as we found some differences in the progression rate with Asian studies using the

same classification. In addition, to our knowledge this is the first multistate analysis of high myopia that allows estimating the probability of macular changes to progress at a given age. Although this kind of statistical study gives us an analysis along the time considering initial status of the macula approaching to a prospective view of the problem, it suggests a compelling need for further prospective, longitudinal studies using multistate models to more accurate characterize the progression probabilities of Myopic Maculopathy, its incidence in visual outcomes, and to identify modifiable associated predictors in different racial setting and/or using more comprehensive classifications.

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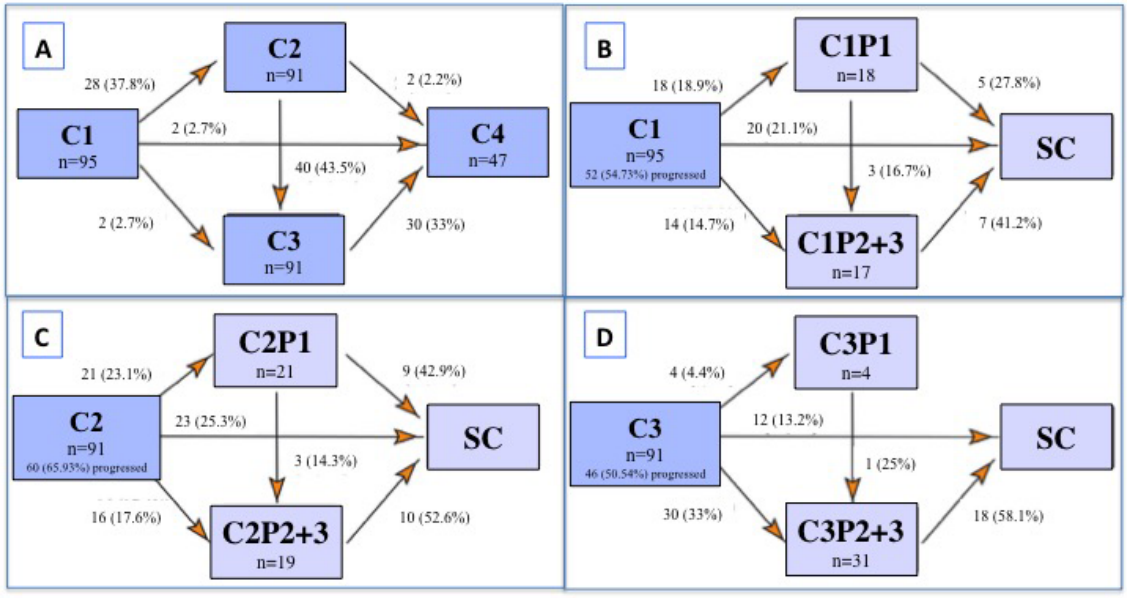
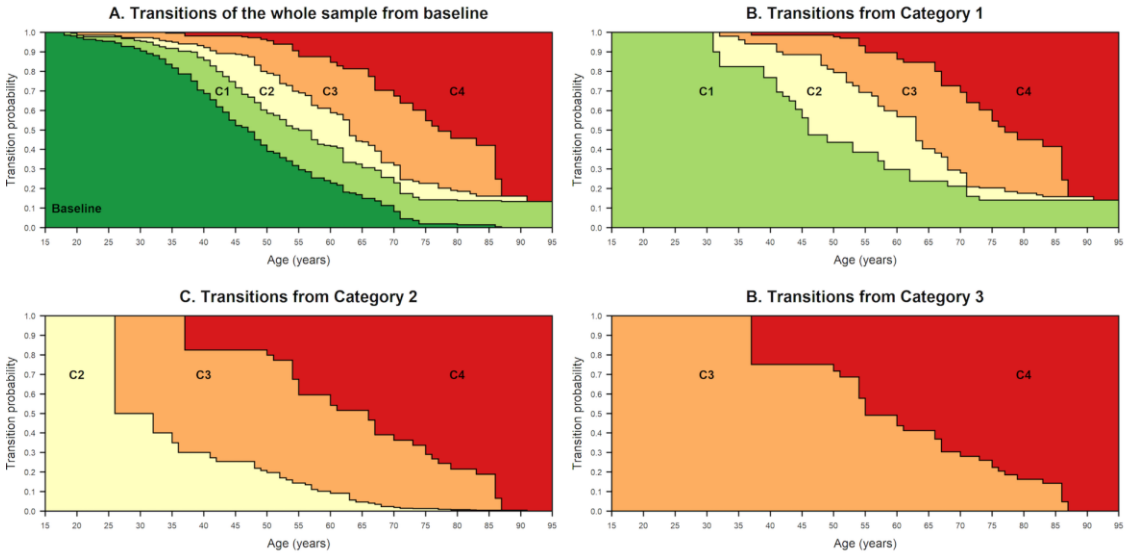
FIGURES WITH FIGURE LEGENDS

Figure 1. Evolution to a Higher Category and/or Plus Sign from Each Initial Category.



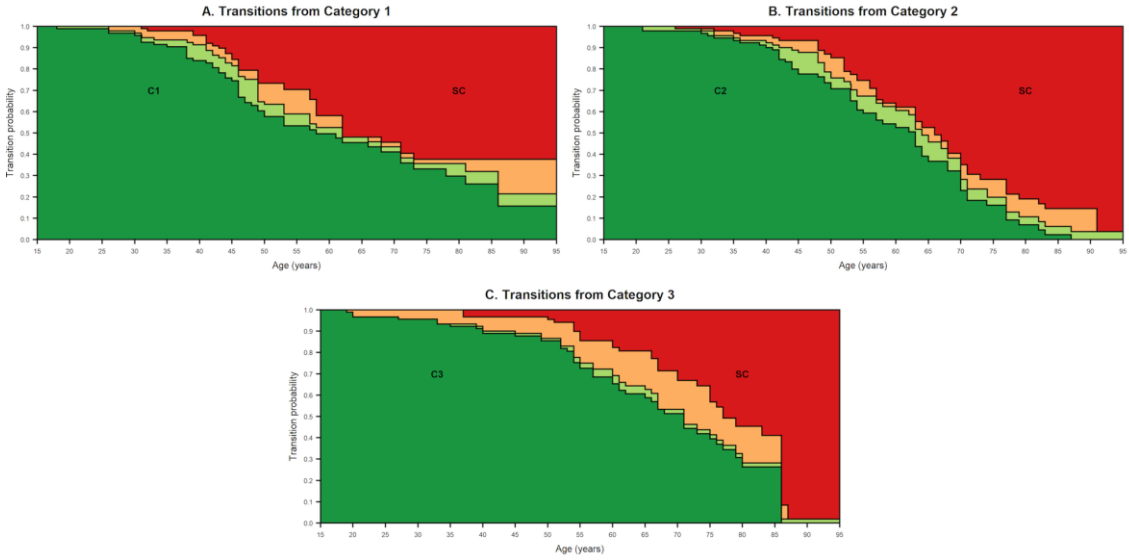
C1=category 1; C2=category 2; C3=category 3; C4=category 4; C1P1=category 1 + plus sign 1; C1P2+3=category 1 + plus sign 2+3; C2P1=category 2 + plus sign 1; C2P2+3=category 2 + plus sign 2+3; C3P1=category 3 + plus sign 1; C3P2+2=category 3 + plus sign 2+3; SC=superior category.
A. Eyes from the whole sample that progressed from another category at any time during follow-up without considering the plus signs. **B.** Eyes starting in category 1 and progressing to a higher category or developing any plus sign; **C.** The same as B but starting at category 2. **D.** The same but starting at category 3.

Figure 2. The Probability of Being in Each Category throughout Life in Highly Myopic Adults.



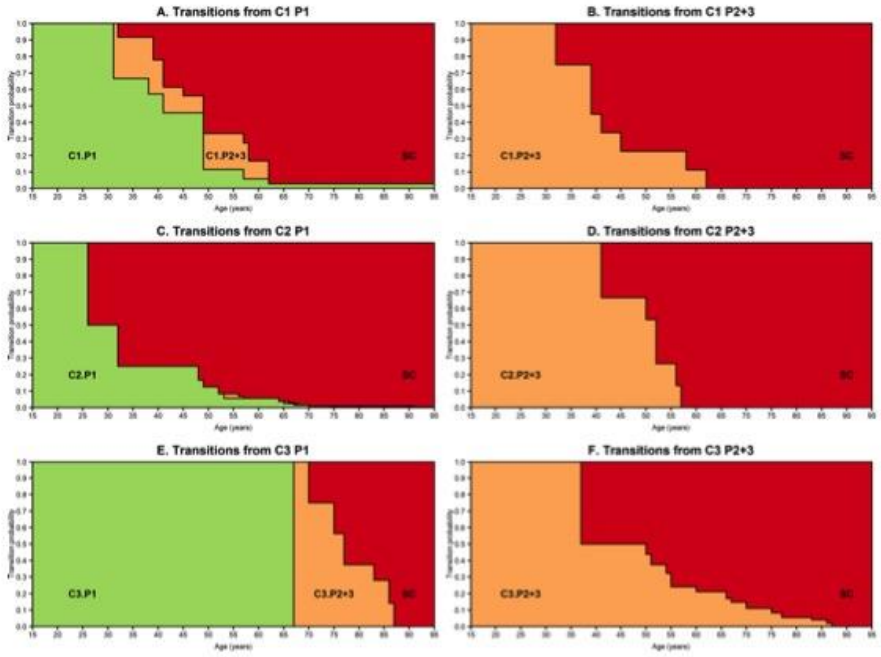
The distance between the adjacent curves represents the probability of being in the corresponding category. **A.** Transitions of the whole sample from baseline. **B.** Transitions only of patients starting at category 1. **C.** Transitions from category 2. **D.** Transitions from category 3.

Figure 3. Estimations of the Probabilities of Transitioning to Any Plus Sign or to a Superior Category.



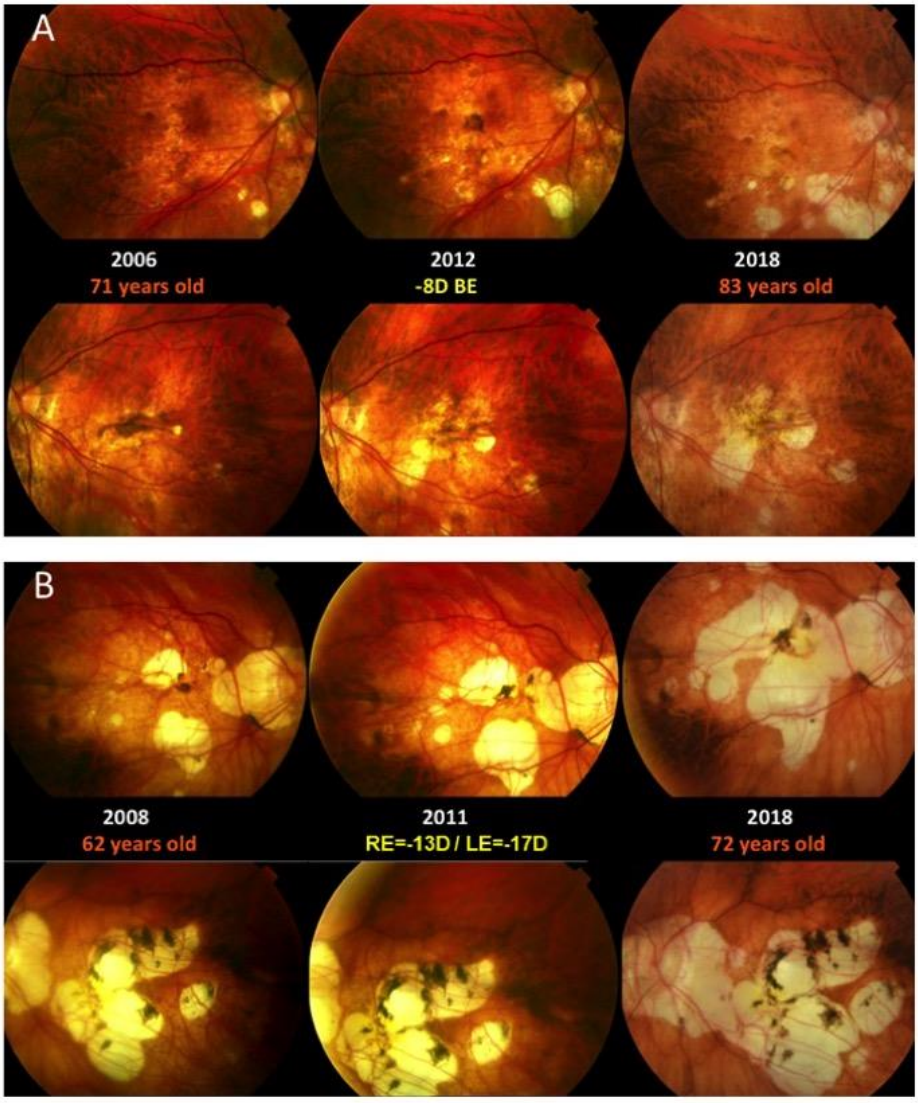
The distance between adjacent curves represents the probability of being in the corresponding category. **A.** Eyes starting from category 1. C=category 1 (dark green); category 1 + plus sign 1 (light green); category 1 + plus sign 2 or 3 (orange); CS= superior category (red). **B.** Eyes starting from category 2. C2=category 2 (dark green); category 2 + plus sign 1 (light green); category 2 + plus sign 2 or 3 (orange); CS= superior category (red). **C.** Eyes from category 3. C3=category 3 (dark green); category 3 + plus sign 1 (light green); category 3 + plus sign 2 or 3 (orange); CS= superior category (red).

Figure 4. Estimations of the Probabilities of Transitioning from Each Category to a Superior Category Considering the Juxtaposition of Plus Signs at Baseline.



The distance between the adjacent curves represents the probability of being in the corresponding category. **A.** Eyes starting from category 1 and plus sign 1. C1P1=category 1 + plus sign 1 (light green); C1P2+3=category 1 + plus sign 2 or 3 (orange); CS=superior category (red). **B.** Eyes starting from category 1 and plus sign 2+3. C1P2+3=category 2 + plus sign 2 or 3 (orange); CS= superior category (red). **C.** Eyes starting from category 2 and plus sign 1. C2P1=category 2 + plus sign 1 (light green); CS= superior category (red). **D.** Eyes starting from category 2 and plus sign 2+3. C2P2+3=category 2 + plus sign 2 or 3 (orange); CS= superior category (red). **E.** Eyes starting from category 3 and plus sign 1. C3P1=category 3 + plus sign 1 (light green); C3P2+3=category 3 + plus sign 2 or 3 (orange); CS= superior category (red). **F.** Eyes starting from category 3 and plus sign 2+3. C3P2+3=category 3 + plus sign 2 or 3 (orange); CS= superior category (red).

Figure 5. Representative Fundus Photographs of Progression.



A. Retinography shows choroidal neovascularization (CNV) in 2006 in the left eye and CNV-related macular atrophy during 12 years of follow-up (top, right eye up; bottom, left eye). The right eye shows category 2 and lacquer cracks developing CNV in 2012 and CNV-related macular atrophy in 2018. **B.** CNV-related macular atrophy in the right eye and multiple patchy atrophies outside the fovea (category 3) and finally involving the fovea (category 4) during 10 years of follow-up on the left eye (top, right eye; bottom, left eye). D=diopters; BE=both eyes; RE=right eye; LE=left eye.

Table 1. Characteristics of the Total Sample at Baseline and the Final Visit.

	Baseline	Final Visit
Age (years)		
Mean ± SD	48.18 ±14.1	60.29 ±13.96
Range	18/87	29/92
Refractive error (diopters) (*P=0.004*)		
Mean ± SD	-13.71±5.33	-14.71±5.69
Range	-30/-6	-33/-6
BCVA in logMAR *(P<0.0001)*		
Mean ± SD	0.38±0.52	0.55±0.65
Range	-0.1/2	-0.1/3
Modified myopic maculopathy according to the META-PM study[5,6]		
Category 0 (normal fundus)	20 (9.1%)	0
Category 1 (tessellated fundus)	74 (33.6%)	63 (28.6%)
Category 2 (diffuse atrophy)	64 (29.1%)	49 (22.3%)
Category 3 (patchy atrophy)	49 (22.3%)	61 (27.7%)
Category 4 (macular atrophy)	13 (5.9%)	47 (21.4%)
Plus sign 1 (lacquer cracks)	22 (10%)	43 (19.5%)
Plus sign 2 (myopic CNV) / Plus sign 3 (Fuchs' spot) ± related macular atrophy	48 (21.9%)	78 (35.5%)

SD = standard deviation; BCVA= best-corrected visual acuity; logMAR=logarithm of minimum angle of resolution; %: percentage; CNV=choroidal neovascularization.

Table 2. Characteristics of the Total Sample Population Subgroups of Highly Myopic Patients with/without Pathologic Myopia, according to the Modified META-PM classification.

Characteristics	Total	With PM† (> Category 2)	Without PM† (Categories 0 and 1)	*P* Value
Number and % of eyes	220	138 (62.7%)	82 (37.3%)	
Baseline age (years)				**0.0018**
Mean ± SD	47.56±14.39	49.78±14.35	43.83±13.77	
Range	18/87	19/87	18/74	
Refractive error				**<0.0001**
Mean ± SD	-13.71±5.33	-15.61±5.3	-10.49±3.57	
Range	-30/-6	-30/-6	-21/-6	
Initial BCVA (logMAR)				**<0.0001**
Mean ± SD	0.38±0.52	0.54±0.57	0.12±0.25	
Range	-0.1/2	-0.1/2	-0.1/2	
Follow-up (years)				0.9169
Mean ± SD	12,73 ±5.81	12.97 ±6.5	12.33 ±4.4	
Range	5/47	5/47	5/21	
Progression rate (per 1000 eyes-year)	**32.21**	**53.84**	**79.18**	

PM= Pathologic Myopia %: percentage; SD= standard deviation; BCAV= best corrected visual acuity; logMar= logarithm of minimum angle of resolution.

† Classified at baseline.

Table 3. Baseline Characteristics of Eyes in Each Category and Plus Signs in Eyes with Pathologic Myopia: ≥ Category 2 and/or Any Plus Sign (n=138)

MM according to the modified META-PM Study	Category 2: (Diffuse Atrophy)	Category 3: (Patchy Atrophy)[b]	Category 4: (Macular Atrophy)	Lacquer Cracks in Any Category	CNV in Any Category
No. of eyes	64	49	13	22	48
Baseline age (years)[a]					
Mean ± SD	50.31±14.44%	51±14.95%	54.46±9.82	47.27±15.3	48.04±16.44[d]
Range	21/87	19/80	34/67	21/74	19/87
Follow-up (years)					
Mean ± SD	11.34±4.29	15.45±8.76	13.23±4.62	10.73±3.93	14.74±9.51
Range	5/27	5/47	9/21	5/18	5/47
Refractive error[a]					
Mean ± SD	-15.11±5.13	-16.43±5,28	-16.56±5.86	-15.32±4.72	-15.62±6.17
Range	-30/-6	-30/-6	-27/-8	-25/-6	-30/-6
Baseline BCVA (LogMAR)[c]					
Mean ± SD	0.4±0.53	0.62±0.56	1.19±0.53	0.32±0.48	0.78±0.6
Range	-0,1/2	0/2	0,7/2	0/2	0/2
Progression rate: per 1000 eyes-year	104.45	163.5	561.83	421.41	393.71

MM: myopic maculopathy, CNV: choroidal neovascularization or Fuch's Spot + Related Macular Atrophy; No: number; SD: standard deviation; BCAV = Best corrected visual acuity; logMAR=logarithm of the minimum angle of resolution.

a There were no statistically significant differences in age or refractive error between the subgroups.

b Category 3 had the longest follow-up.

c The initial BCVA was significantly worse in category 4 than in category 2 (P<0.0001) and category 3 (P=0.0027).

d The BCVA also was worse in plus sign 2+3 than in plus sign 1 (P=0.0022).

TABLE 4. Comparison of Our Series with Asian Series of Highly Myopic Patients.

Authors and Countries	Fang et al.[6] (Japan)	Hayashi et al.[12] (Japan)	Yan et al.[13] (China)	Coco et al. (Spain)
No. of eyes (patients)	810 (432)	806 (429)	110 (71)	220 (122)
Baseline age (years)				
Mean±SD	42.3±16.8	41.1±16.7	56.2±9.5	48.18 ±14.1
Range	3/85	4/74	40/78	18/87
Refractive error				
Mean±SD	-13.3±4.8	-13.4±4.9	-9.53±3.7	-13.71±5.33
Mínimum	≥-8	≥-8	≥-6	≥-6
Follow-up (years)				
Mean±SD	18.7±7.1	12.7±6.2	10	12.11±4.62
Mínimum	10	5	10	5
Eyes progressing		40,6%	35,5%	69,1%
Progression from category 1		13,4%	19%	54.73%
Progression from category 2	63.7%	49.2%	71%	65.93%
Progression from category 3	97.4%	70.3%	100%	50.54%
Patterns of progression (%)				
Change from Peripapillar atrophy to Category 2	31.6%			
Category 1 changing to 2		10.1%	15%	37.8%
Category 1 developing LCs		2.9%	1%	18.9%
Category 1 developing CNV		0.4%	0%	14.7%
Category 2 changing to 3	53.2%	19.4%	13%	43.5%
Category 2 developing LCs	5%	2.2%		23.1%
Category 2 developing CNV	16.2%	1.6%	4%	17.6%
Category 3 changing to 4	4.4%			8.3%
LCs progressing to category 3	57.6%	42.7%		
LCs developing CNV		13.3%		16.27%
CNV progressing to category 4	92.7%	90.1%		
Progression in per 1000 eyes-year				
Total sample	47			32.21
Eyes with MM	75.3			53.84
Eyes without MM	18.1			79.18

No=number; SD=standard deviation; %=percentage; MM=myopic maculopathy; LCs=lacquer cracks; CNV= choroidal neovascularization and/or Fuch's spot ± related atrophy.