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Risk factors for the progression of age-related macular degeneration in patients of the Ukrainian population

S. Yu. Mogilevskyy, T. S. Zavgorodnia

Shupyk National Healthcare University of Ukraine

Kyiv (Ukraine)

Background: *Researchers need to find informative age-related macular degeneration (AMD) criteria which could be used for developing expert systems for the prediction of the course of the disease.*

Purpose: *To evaluate risk factors of AMD progression on the basis of clinical and ophthalmological characteristics in patients of the Ukrainian population.*

Material and Methods: *Totally, 302 eyes (152 patients) with AMD were included in the study. The stage of AMD was determined based on the Age-related Eye Disease Study (AREDS) guidelines. Median patient age (95% confidence interval (CI)) was 71.18 (69.47 – 72.89) years, most (82.9%) patients were of 60 – 85 years, and the percentage of women was 59.9%. Visual acuity, best-corrected visual acuity (BCVA), numbers of small, intermediate and large drusen, presence of retinal pigment epithelium (RPE) changes, subretinal neovascular membranes (SNM), and geographic RPE atrophy were assessed at baseline and at 1 year and 2 years. Statistical analyses were conducted using MedStat and MedCalc v.15.1 (MedCalc Software bvba, Ostende, Belgium) and EZR v.1.64 software (R Foundation for Statistical Computing, Austria).*

Results: *There was a slow but statistically significant reduction in median BCVA (interquartile range (IQR)) from 0.4 (0.1–0.85) at baseline to 0.325 (0.1 – 0.8) ($p < 0.001$) at 2 years. Over the first year and over the second year, the frequency of RPE changes increased by 6.3% and 10.9%, respectively ($p < 0.001$), the frequency of SNM detection increased by 13.3% and 21.2%, respectively ($p < 0.001$), and the frequency of geographic atrophy detection, by 5.7% and 8.0%, respectively ($p < 0.001$). A multivariate logistic regression model was developed to select four covariates for the risk of AMD progression (the male gender, BCVA, number of small drusen and AREDS category at baseline). The BCVA was negatively associated ($p = 0.026$; OR = 0.12; 95% CI, 0.03 – 0.60), whereas the number of small drusen was positively associated with the risk of AMD progression ($p = 0.009$; OR = 1.02; 95% CI, 1.00–1.04). The risk of AMD progression was the highest for eyes with the AREDS category 2 (63.0%, 95% CI, 48.7% – 75.7 %), and the lowest for eyes with the AREDS category 3 (41.2 %, 95% CI, 29.4% – 53.8%, $p = 0.049$).*

Conclusion: *First, over 24 months, we observed a slow but statistically significant reduction in visual acuity, with an increase in the frequency of RPE changes and detection of SNM and geographic atrophy. Second, a multivariate logistic regression model was developed to select four covariates for the risk of AMD progression (the male gender, BCVA, number of small drusen and AREDS category at baseline). The BCVA was negatively associated, whereas the number of small drusen was positively associated with the risk of AMD progression. Finally, the risk of AMD progression was the highest for eyes with the AREDS category 2, and the lowest for eyes with the AREDS category 3.*

Keywords:

AREDS, visual acuity, drusen, RPE changes, subretinam neovascular membrane, geographic atrophy, model of disease progression

Introduction

Age-related macular degeneration (AMD) is the most common cause of blindness in developed countries, and its prevalence is likely to increase as a consequence of exponential population aging [1]. In a review and meta-analysis of Wang and colleagues (2014) [1], the pooled prevalence (mapped to an age range of 45-85 years) of any AMD was 8.69%, and they found a higher prevalence of any AMD in Europeans than in Asians or Africans (12.3% versus 7.4%). The projected number of people with AMD in 2040 was 288 million (95% confidence interval (CI), 140 – 261) [1].

Jin and colleagues (2019) [2] reported that the crude pooled prevalence of early and late AMD among Caucasian populations was 10.1% (95% CI, 5.7% – 17.2%) and 1.6% (95% CI, 1.0% – 2.4%), and among Chinese populations worldwide aged 50 years and above, 4.9% (95% CI, 3.1% – 7.7%) and 0.7% (95% CI, 0.5% – 1.1%), respectively.

AMD was described as an exaggerated form of retinal aging, compared to a physiological decline in retinal function observed in elderly people [3].

Early dry AMD is characterized by the presence of soft drusen and changes in the Bruch's membrane, choriocapillaris, retinal pigment epithelium (RPE), and photoreceptors. The characteristic features of late dry AMD are geographic atrophy, epithelial pigment detachment, subretinal neovascularization, hemorrhage and fibrous scars. Neovascular (wet) AMD is used to describe macular degeneration with choroidal neovascularization (CNV). This type affects 10% of AMD patients, but accounts for about 90% of cases with severe vision loss associated with the disease [4].

Asymptomatic course is typical for early (and sometimes late) AMD [5]. Late diagnosis of AMD contributes to poorer vision and certain difficulties in treatment, whereas early initiation of multicomponent therapy may arrest disease progression [6].

Solving the issues of early diagnosis and finding novel biomarkers of the disease are important and will enable the utilization of more rational approaches to treatment [7].

Given the above, informative disease criteria (particularly, those for screening) should be looked for [8]. Rizaiev and colleagues [6] found that AMD risk factors include advancing age, gender, race, current smoking, iris color, obesity, arterial hypertension, diabetes mellitus and previous cataract surgery.

Recently, reports have appeared on predictive expert systems which propose biomarker assessment-based AMD progression models [9, 10]. For AMD eyes with large drusen and no advanced disease, a novel risk assessment model has been built based on age and spectral-domain optical coherence tomography (SD-OCT) segmentation, drusen characteristics, and retinal pathology – for progression of CP-visible GA over up to 5 years [9].

The purpose of the current study was to evaluate risk factors of AMD progression on the basis of clinical and ophthalmological characteristics in patients of the Ukrainian population.

Material and Methods

This was a prospective, clinical observational study. The study followed the ethical standards stated in the Declaration of Helsinki of 1964 (as amended), the European Convention on Human Rights and Biomedicine and relevant laws of Ukraine, and was approved by the Ethics Committee of the Shupik National Healthcare University of Ukraine. Informed consent was obtained from all study subjects.

The study included male and female patients with AMD who were 40-89 years of age. Excluded were patients on anti-vascular-endothelial-derived growth factor (VEGF) treatment for AMD; those with any diabetes, history of eye surgery or trauma, retinal vascular disease, ocular inflammation; current central serous choriopathy, other macular degenerations, aphakia, chronic infection or intoxication of any kind, ear, nose of throat (ENT) disease, dental or jaw disease, cancer, blood disorders, kidney disease, those with alcohol or drug addiction, history of radiation exposure and pregnant women.

Totally, 302 eyes (152 patients) with AMD were included in the study. Disease level was classified based on the category of AMD in the patient's worse eye: AREDS category 1 (no AMD) consisted of fewer than 5 small (<63 μm) drusen; category 2 (mild AMD), multiple small drusen, non-extensive intermediate (63 – 124 μm) drusen, pigment abnormalities, or a combination; category 3 (intermediate AMD), at least 1 large (>125 μm) druse, extensive intermediate drusen, or geographic atrophy not involving the center of the macula; and category 4 (advanced AMD), central geographic atrophy or neovascular AMD in 1 eye or visual loss resulting from AMD, regardless of the lesion type [11].

In the current study, there were 60 eyes with AREDS category 1, 54 eyes with AREDS category 2 (early AMD), 68 eyes with AREDS category 3 (intermediate AMD), and 120 eyes with AREDS category (late AMD). All patients received medical therapy as per AREDS 2.

They had a conventional eye examination including visual acuity, static Humphrey perimetry, refractometry, intraocular pressure (IOP) measurement, biomicroscopy, gonioscopy, and ophthalmoscopy with Volk Super Field lens and Goldmann three-mirror lens (Volk Optical, Mentor, OH). In addition, spectral domain optical coherence tomography (SD-OCT) and OCT (Retina Angio mode) were performed. Fundus photography study with a fundus camera was conducted. Fluoresecein angiography (FA) was performed with the fundus camera if (a) mild vitreoretinal neovascularization or proliferation was suspected but not identified with ophthalmoscopy or fundus photography or (b) the visual function did not correspond either to ophthalmoscopic changes in the macula or OCT findings.

Mean patient age was 71.18 years (95% CI, 69.47 – 72.89 years), and most (82.9%) patients were of 60 – 85 years. The percentage of women was 59.9%, and men, 40.1%. There was no significant difference between disease stages or age categories in terms of gender distribution ($p > 0.1$).

Overall, 31.6% of patients with AMD were smokers, and percentages of smokers among male and female patients were 79.2 % and 20.8%, respectively. In all study eyes, visual acuity, best-corrected visual acuity (BCVA), numbers of small, intermediate and large drusen, presence of retinal pigment epithelium (RPE) changes, subretinal neovascular membranes (SNM), and geographic RPE atrophy were assessed at baseline, at 1 year and at 2 years.

Statistical analyses were conducted using MedStat and MedCalc v.15.1 (MedCalc Software bvba, Ostende, Belgium) software [12]. The normal distribution of data was tested with the Kolmogorov-Smirnov test. Median and interquartile range (IQR) values were used for the descriptive statistics analysis because the distribution was not normal. Kruskal–Wallis test was used for

continuous variables, and the $\chi 2$ test or Fisher's exact test for categorical variables, as appropriate, followed by Bonferroni's correction or Dunn's post-hoc testing for multiple comparisons.

The analysis of risk factors for the deterioration of the state of the eye was conducted in 182 eyes which had AREDS categories 1 to 3 at baseline. Logistic regression models were developed for analysis. An increase in the AREDS category was considered a deterioration in the state of the eye (variable Y = 1). In 2 years, 95 eyes showed a deterioration in the state of the eye (variable Y = 1), and 87, no change in the state of the eye (variable Y = 0). A stepwise approach was used to select independent variables for inclusion or exclusion (inclusion threshold, $p < 0.1$; exclusion threshold $p > 0.2$) and build multivariate logistic regression models. EZR v.1.64 software (R statistical software version 4.3.1 with the R commander package, R Foundation for Statistical Computing, Vienna, Austria) was used [13]. Beta coefficients of models, the significance of the odds ratio (OR) difference from 1, OR and confidence interval (CI) values were calculated.

Patients were followed for 24 months.

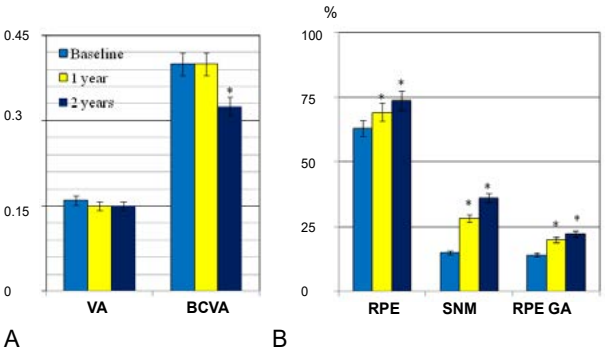

Fig. 1. Visual acuity (VA), best-corrected visual acuity (BCVA) (A), and frequencies of retinal pigment epithelial (RPE) changes and detection of subretinal neovascular membrane (SNM) and geographic atrophy (GR) of the RPE.

Note: *, $p < 0.05$ for comparison to baseline. The ordinate displays visual acuity (A) and percentage frequencies of changes (B).

Results

There was a slow but statistically significant decrease in visual acuity and BCVA (no change or decrease in visual acuity and BCVA) in patients with AMD over the follow-up (Fig. 1A). Median BCVA (IQR) at 12 months was not substantially different from baseline levels (0.4 (0.1 – 0.8) versus 0.4 (0.1 – 0.85)). At 24 months, however, the median BCVA (IQR) decreased to 0.325 (0.1 – 0.8) ($p < 0.001$).

In addition, ophthalmological characteristics deteriorated over the follow-up period (Fig. 1B). The frequency of RPE changes increased by 6.3% over the first year and by 10.9% over the second year ($p < 0.001$) compared to baseline values. In addition, over the first year and over the second year, the frequency of SNM detection increased by 13.3% and 21.2%, respectively ($p < 0.001$), and the frequency of geographic atrophy detection, by 5.7% and 8.0%, respectively ($p < 0.001$).

There was a change in the number of drusen in eyes with AMD over the follow-up period (Fig. 2). The median number of small drusen (IQR) tended to decrease (10 (4 – 19) at baseline, 10 (4 – 19) at month 12, and 9 (2–16) at month 24; $p < 0.001$). There was a statistically significant change in the number of large drusen, but not the number of intermediate drusen (Fig. 2).

A univariate regression analysis of the risk of AMD progression was conducted taking into account the data obtained (Table 1). An increase in the AREDS category was considered evidence of AMD progression (Y = 1), and no increase in the AREDS category (Y = 0), evidence of the absence of AMD progression.

Our univariate regression analysis of the risk of AMD progression demonstrated that no independent variable had a significant association with the risk of the deterioration of the state of the eye ($p > 0.05$). Correspondingly, no calculation of the model OR value or 95% CI was performed.

At the next phase of the analysis aimed at detecting a set of independent variables associated with the risk of the deterioration of the state of the eye, we developed multivariate logistic regression models (Table 2). Four covariate risk factors were selected: the GENDER, BCVA, NUMBER OF SMALL DRUSEN, and AREDS CATEGORY.

The model of the risk of AMD progression developed using the selected covariate risk factors was adequate ($\chi 2 = 22.3$, $p = 0.001$ for the model associated with five degrees of freedom):

$$\ln(Y/(1 - Y)) = 1.61 + 0.58 \times X1 - 2.05 \times X2 + 0.022 \times X3 - b4 \times X4 \quad (1),$$

where X1 is the GENDER (X1 = 0 for Female Gender and X1 = 1 for Male Gender),

X2 is the BCVA,

X3 is the NUMBER OF SMALL DRUSEN, and

X4 is AREDS CATEGORY (1, 2 or 3),

b4 = 0 for AREDS Category 1;

b4 = -0.19 for AREDS Category 2;

b4 = -1.89 for AREDS Category 3.

Male gender increased the risk of AMD progression (OR = 1.78; 95% CI, 0.95–3.44). Correspondingly, although most patients with AMD were women (women, 59.9%; men, 40.1%; the female to male ratio, 3:2), men exhibited greater disease progression compared to women.

The BCVA was negatively associated with the risk of AMD progression ($p = 0.026$; OR = 0.12; 95% CI, 0.03–0.60), whereas the NUMBER OF SMALL DRUSEN was positively associated with the risk of AMD progression ($p = 0.009$; OR = 1.02; 95% CI, 1.00 – 1.04).

The receiver operating characteristic (ROC) curve of the model is shown in Fig. 3. An area under curve (AUC)

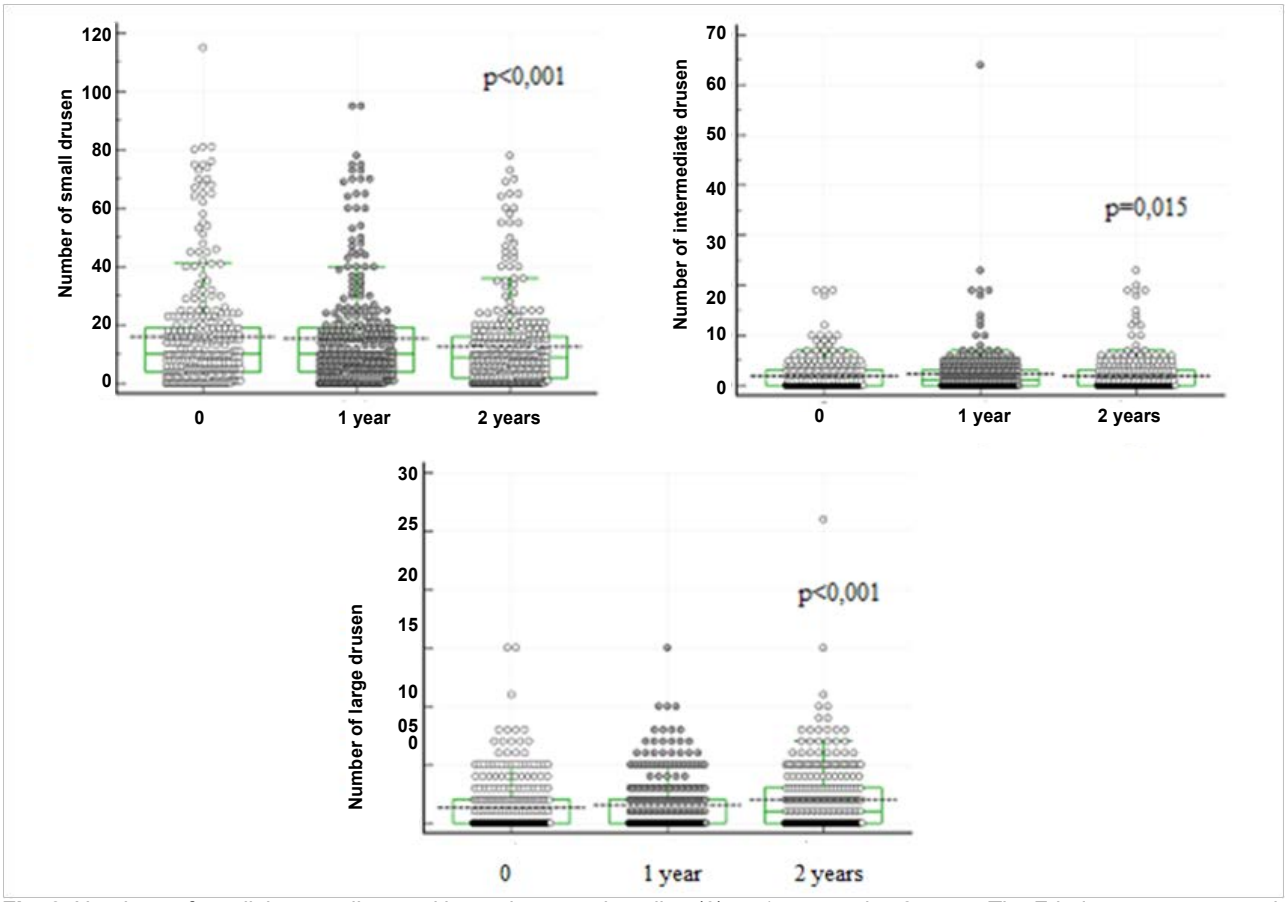

Fig. 2. Numbers of small, intermediate and large drusen at baseline (0), at 1 year and at 2 years. The Friedman test was used for paired samples

Table 1. Analysis of univariate logistic regression models for predicting the risk of age-related macular degeneration (AMD) progression

Independent variable		Model coefficient, b ± m	Significance of the odds ratio (OR) difference from 1, p	Median odds ratio (95% confidence interval) for the model
Gender	Female	Reference		
	Male	0.48±0.30	0.114	–
Smoking	No	Reference		
	Yes	0.42±0.35	0.229	–
Age		0.004±0.014	0.799	–
Visual acuity		-0.08±0.47	0.861	–
BCVA		-0.39±0.50	0.432	–
Small drusen, for each druse		0.015±0.092	0.092	–
Intermediate drusen, for each druse		-0.049±0.047	0.300	–
Large drusen, for each druse		-0.10±0.08	0.203	–
RPE changes	No	Reference		
	Yes	-0.33±0.31	0.266	–
Geographic atrophy	No	Reference		
	Yes	0.62±0.88	0.477	–
AREDS category		-0.29±0.18	0.105	–

Table 2. Analysis of the 4-variate logistic regression model for predicting the risk of age-related macular degeneration (AMD) progression

Independent variable		Model coefficient, b ± m	Significance of the odds ratio (OR) difference from 1, p	Median odds ratio (95% confidence interval) for the model
Gender	Female	Reference		
	Male	0.58±0.32	0.073	1.78 (0.95 – 3.44)
Best-corrected visual acuity (BCVA)		-2.05±0.78	0.026	0.12 (0.03 – 0.60)
Small drusen, for 1		0.022±0.010	0.009	1.02 (1.00 – 1.04)
AREDS category	1	Reference		
	2	-0.19±0.43	0.661	–
	3	-1.89±0.57	0.001	0.15 (0.05 – 0.46)

of 0.69 (95 % CI, 0.62 – 0.76) indicated the presence of an association of the risk of the deterioration of the state of the eye with the GENDER, BCVA, NUMBER OF SMALL DRUSEN and AREDS CATEGORY. The model had a sensitivity of 82.1% and a specificity of 50.6%.

Because different AREDS categories resulted in different rates of AMD progression, a separate analysis of the percentage of eyes with AMD progression was required (Fig. 4). The median percentage of eyes with AMD progression (IQR) for eyes with AREDS category 1 was 55.0 % (95% CI, 41.6%–67.9 %), eyes with AREDS category 2, 63.0 % (95% CI, 48.7%–75.7%), and eyes with AREDS category 3, 41.2 % (95% CI, 29.4%–53.8 %). These data reflected the risk of AMD progression in different stages, and the difference was statistically significant (p = 0.049).

Therefore, there was a slow deterioration in visual acuity and an increase in the severity of retinal changes in eyes with AMD over the follow-up period. Our multivariate regression analysis found four risk factors important for the progression of AMD over 24 months: male gender, BCVA, number of small drusen and AREDS category.

Discussion

It has been found that men have a greater risk of AMD progression compared to women. However, it has been demonstrated in multiple studies that AMD is more frequently seen in females than males [14, 15], and in our

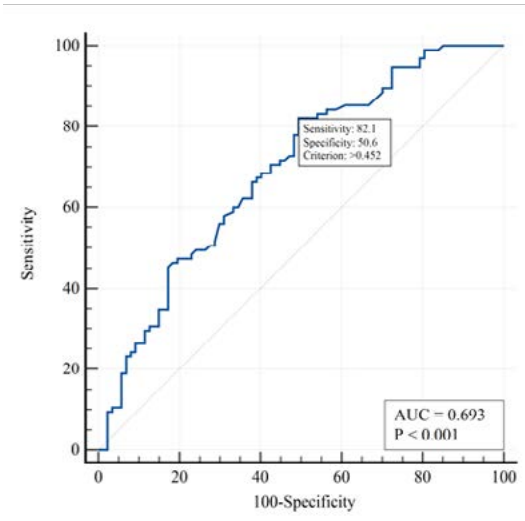

Fig. 3. Receiver operating characteristic (ROC) curve of the four-variate logistic regression model for predicting the risk of the deterioration of the state of the eye. Sensitivity and specificity are specified for the threshold selected on the basis of Youden's Index (Y_{crit} = 0.452)

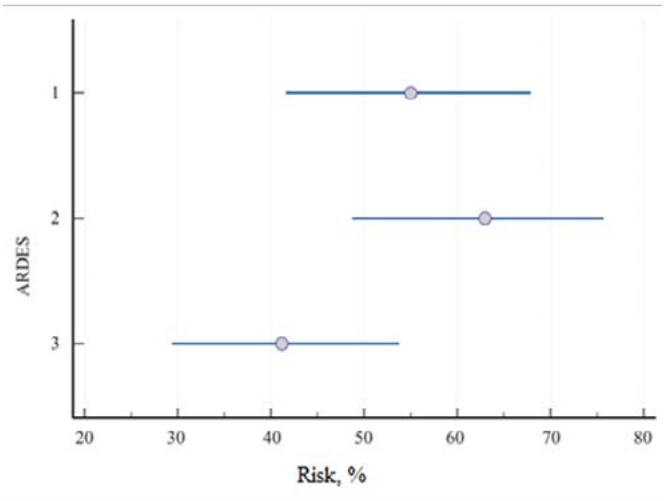

Fig. 4. Risk of an increase in the AREDS category (expressed in median percentage and 95% confidence interval) for eyes differing in their status at baseline (χ2 p = 0.049)

study, the female to male ratio was 3:2. Therefore, the comparison of our findings with previous studies showed that AMD more frequently developed in females, but males more frequently exhibited AMD progression.

A greater susceptibility to AMD progression in males could be associated with smoking [16]. Patients with dry AMD have been found to have a greater risk of smoking-associated mortality compared to patients without dry AMD [17]. In the current study, of the total patients with AMD, 31.6% were smokers, but of the total smokers, most (79.2 %) were males. Therefore, it can be said that smoking is one of the causes of greater AMD progression in males than in females.

In addition, others [17] have reported age is another factor of the risk of AMD; we, however, found no association between the age and AMD progression.

Aging of the eye is accompanied by the buildup of uncleared cellular debris that originates from the RPE and accumulates where the RPE interfaces with Bruch's membrane and the neurosensory retina [18]. These deposits, known as drusen, typically are the first ophthalmoscopic sign of AMD, appearing before visual function is appreciably affected. Drusen are composite structures, primarily consisting of lipids as well as proteins and carbohydrates that can be visualized as small white or yellowish deposits on the macula [18, 19].

Drusen deposition in Bruch's membrane concomitant with persistent activation of the complement cascade and inflammation lead to thickening and decreased permeability of the membrane. This obstructs both nutrient transport to the retina and waste exchange to the choroid and is accompanied by thinning of the choroidal vasculature [20]. These steps, combined with neurodegenerative changes within the photoreceptor-RPE complex, result in pigmentary abnormalities of the RPE, including hypo or hyperpigmentation, in early or intermediate stages of AMD.

Drusen aggregate and undergo morphologic changes during AMD progression. Small, well-defined drusen particles, referred to as hard drusen, are common in younger individuals and are not a sign of AMD risk [21]. Soft drusen are less demarcated and grow over time, coalescing into confluent drusen, and co-occurring with AMD. Eventually, soft drusen mature to a crystalline form, which is predictive of graphic atrophy.

In the current study, it is small drusen that were identified as a risk factor of AMD progression with OR =1.02 for each druse. As it is mentioned above, the formation of drusen occurs before a clinical reduction in visual acuity, and triggers a pathological cascade of events that is completed by the death of RPE and photoreceptor cell death.

An interesting finding of the current study was that the AMD progression over two years depended on the AREDS category at baseline. Eyes with the AREDS category 1 at baseline had the highest risk (50%), and eyes with the AREDS category 3, the lowest risk of AMD progression. Thomas and colleagues [22] found that there is a 25% risk of early AMD and 8% risk of late AMD in patients over the age of 75. These results confirm that eyes which differ in the stage of AMD also differ in the rate of AMD progression. We found that the rate of AMD progression was higher in the early disease and decreased with time. This is likely to be caused by the morphogenesis of small drusen, with their number fast increasing in the early stage, causing a transition from early to intermediate disease, whereas the involvement of multiple pathological cascades in the retina occurs more slowly, which ultimately results in geographic atrophy.

Reticular pseudodrusen, hyperreflective foci, and drusen sub-phenotypes are known as risk factors for progression towards late-stage disease [23], and we believe that multimodal imaging studies of these biomarkers are promising. The determination of the significance of these biomarkers would improve the quality of the prediction of AMD progression.

Shin and colleagues [24] aimed to develop a risk prediction model for the progression of AMD in Koreans using systemic and environmental factors. Their model included the male gender, drusen location, size and number, and hyperpigmentation or hypopigmentation as factors, which is in agreement with our findings.

The potential of the individualized prediction based on the determination of certain biomarkers has been confirmed by predictability of the risk of poor efficacy of late AMD treatment with intravitreal anti-VEGF injections [10]. A smart phone-based rapid assessment with a machine learning approach using adaptive neuro-fuzzy inference system of two-sample prediction model has been presented that requires only the baseline measurements and changes in visual acuity (VA) as well as macular thickness (MAC) after four months of treatment to estimate the values of VA and MAC at 8 and 12 months. The model has shown to have a very high accuracy (> 92%) and works in near-real-time scenarios [10].

The formula we have developed (1) allows predicting the progression of AMD at different initial stages on the basis of a small number of factors, too.

Conclusion

First, over 24 months, we observed a slow but statistically significant reduction in visual acuity, with an increase in the frequency of RPE changes and detection of SNM and geographic atrophy.

Second, a multivariate logistic regression model was developed to select four covariates for the risk of AMD progression (the male gender, BCVA, number of small drusen and AREDS category at baseline). The BCVA was negatively associated, whereas the NUMBER OF SMALL DRUSEN was positively associated with the risk of AMD progression.

Finally, the risk of AMD progression was the highest for eyes with the AREDS CATEGORY 2, and the lowest for eyes with the AREDS CATEGORY 3.

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