Non-Exudative Macular Neovascularization: A 2-Year Follow-up Study Assessing the Progression of Retinal Pigment Epithelium and Outer Retinal Atrophy

Neovascularização Macular Não Exsudativa: Avaliação a 2 Anos da Progressão da Atrofia do Epitélio Pigmentar da Retina e Retina Externa

Ana Margarida Ferreira [1], Rodrigo Vilares-Morgado [1,2], Rita Rodrigues [1], Ângela Carneiro [1,2], Manuel Falcão [1,2]

[1] Ophthalmology Department, ULS São João, Porto, Portugal
[2] Surgery and Physiology Department, Faculty of Medicine of University of Porto, Porto, Portugal

Recebido/Received: 2024-10-18 | **Aceite/Accepted:** 2025-10-29 | **Published online/Publicado online:** 2026-03-17 | **Publicado/Published:** 2026-03-25

DOI: https://doi.org/10.48560/rspo.38320

ABSTRACT

INTRODUCTION: Advanced age-related macular degeneration (AMD) includes exudative and atrophic phenotypes. Non-exudative macular neovascularization (NE-MNV) has been linked to smaller areas of geographic atrophy (GA), suggesting it may slow the progression of complete retinal pigment epithelium and outer retinal atrophy (cRORA). This study aims to determine whether NE-MNV affects the prevalence and progression of cRORA over two years.

METHODS: This observational study included 65 patients with unilateral exudative AMD, assessing 2-year cRORA progression and exudative conversion in the fellow eye. Patients were grouped based on the presence (NE-MNV) or absence (no NE-MNV) of NE-MNV. The prevalence and progression of tomographic cRORA, GA on fundus autofluorescence (FAF), cRORA greatest linear diameter (GLD), GA area, and exudative conversion rates were compared.

RESULTS: Sixty-five patients were included in our cohort. The prevalence of NE-MNV was 24.6% (n=16). We identified a 33% bilateral exudative conversion rate (n=4) in the NE-MNV group and a 16.9% conversion rate in the eyes without NE-MNV (n=9) over the 2-year period (p=0.036). Eyes with NE-MNV had proportionally more frequent tomographic signs of atrophy (47.3% *vs* 31.3% in eyes without NE-MNV; p=0.535) and a smaller cRORA GLD (958.50±348 *vs* 2629.46±2124.72, p=0.008) compared to eyes without NE-MNV. cRORA was present in 11 eyes (30.6%) without NE-MNV and 2 eyes (12.5%) with NE-MNV (p=0.118). There were no significant differences in FAF GA prevalence (2 eyes out of 16 and 11 eyes out of 36, respectively; p=0.118) or GA area (p=0.186) or GA progression rate (p=0.125) between groups.

CONCLUSION: In our study, the presence of NE-MNV was not associated with the prevalence of cRORA and/or FAF GA after a 2-year follow-up. Nonetheless, eyes with NE-MNV presented smaller cRORA GLD, corroborating that NE-MNV may prevent the progression of cRORA. One-third of the eyes with NE-MNV converted to exudative AMD over 2 years. Extended monitoring is required to confirm these results at long term.

KEYWORDS: Geographic Atrophy; Macular Degeneration; Retinal Pigment Epithelium; Tomography, Optical Coherence; Visual Acuity.

RESUMO

INTRODUÇÃO: A presença de neovascularização macular não exsudativa (NVM-NE) tem sido associada a menores áreas de atrofia geográfica (AG) e a menor progressão para atrofia completa do epitélio pigmentar da retina e retina externa (cRORA). O presente estudo procurou estabelecer se a presença de NVM-NE influencia a prevalência e a progressão de cRORA ao longo de 2 anos.

MÉTODOS: Trata-se de um estudo observacional que incluiu 65 doentes com DMI exsudativa unilateral e que avaliou a progressão de cRORA ao longo de 2 anos e a conversão para DMI exsudativa no olho contralateral. Os doentes foram agrupados com base na presença ou ausência de NVM-NE no olho de estudo na baseline. Foram comparadas a prevalência e progressão da cRORA no OCT e na autofluorescência do fundo (FAF), assim como a variação do maior diâmetro linear da cRORA (MDL) e da área da AG.

RESULTADOS: Do total de 65 olhos incluídos no nosso estudo, a prevalência de NVM-NE foi de 24,6% (n=16). Identificamos uma taxa de conversão para DMI exsudativa bilateral de 33% (n=4) no grupo com NVM-NE no início do estudo, e uma taxa de conversão de 16,9% nos olhos sem NVM-NE (n=9) ao longo do período de 2 anos (p=0,036). Olhos com NVM-NE apresentaram sinais tomográficos de atrofia proporcionalmente mais frequentes (47,3% *vs* 31,3% em olhos sem NVM-NE; p=0,535) e um menor MDL de cRORA (958,50±348 *vs* 2629,46±2124,72; p=0,008). cRORA foi identificado em 11 olhos (30,6%) sem NVM-NE e em 2 olhos (12,5%) com NVM-NE (p=0,118). Não foram encontradas diferenças estatisticamente significativas na prevalência de AG na FAF (2 em 16 *vs* 11 em 36 olhos, respetivamente; p=0,118), na área média da AG (p=0,186) ou na taxa de progressão da AG (p=0,125) entre grupos.

CONCLUSÃO: A presença de NVM-NE não apresenta associação com a prevalência de cRORA e AG após 2 anos de seguimento. No entanto, olhos com NVM-NE apresentaram menor MDL de cRORA, corroborando a hipótese de que este tipo de neovascularização pode atrasar a progressão de cRORA. Um terço dos olhos com NVM-NE converteu para DMI exsudativa em 2 anos.

PALAVRAS-CHAVE: Acuidade Visual; Atrofia Geográfica; Degenerescência Macular; Epitélio Pigmentado da Retina; Tomografia de Coerência Óptica.

INTRODUCTION

Age-related macular degeneration (AMD) represents the most common cause of irreversible blindness in people over 60 years old in developed countries. Age-related cellular, metabolic and mitochondrial malfunction contribute to the progression of central retina degeneration observed in AMD.[1,2] AMD is characterized by the accumulation of extracellular deposits, including subretinal drusenoid deposits, basal linear, and basal laminar deposits. Advanced stages of AMD include both the neovascular (wet) and atrophic (dry) phenotype.[3,4]

Macular neovascularization in AMD implies the presence of neovascular disease in the macula, with the invasion of vascular and associated tissues into the outer retina, subretinal space, or sub- retinal pigment epithelium (RPE) space in varying combinations (depending on the type of MNV).[5,6]

Exudative macular neovascularization associated with AMD is characterized by the presence of leakage of fluid and serum components from a lesion (breakdown of the blood–retinal barrier), associated with the symptomatic presence of macular intraretinal and subretinal fluid. The presence of fluid established on structural optical coherence tomography (OCT) imaging currently guides the treatment decisions using vascular endothelial growth factor (VEGF) inhibitors.[7,8]

Atrophic AMD represents an irreversible stage of the disease, associated with loss of photoreceptors, RPE and choriocapillaris in the macula. It manifests as geographic atrophy (GA) and is associated with a permanent impact in visual acuity. Currently, there are no specific treatments approved for dry AMD, although emergent potential treatment options are now under investigation in numerous clinical trials for the reduction in GA lesion growth.[9]

In recent years, there has been a huge effort to identify potential predictors and biomarkers associated with the progression of AMD to advanced stages of the disease.

Non-exudative macular neovascularization (NE-MNV) represents an asymptomatic stage of AMD and it is considered to be a precursor for exudative AMD, while representing a protective factor for atrophy phenotype, associated with smaller areas of GA and slower progression of RPE and outer retinal atrophy (cRORA).[10]

Vilares-Morgado *et al* conducted an observational cross-sectional study of 68 patients with unilateral exudative AMD, aiming to establish if the presence of NE-MNV influences the prevalence of RPE and outer retinal atrophy

in eyes with AMD. The authors concluded that the presence of NE-MNV was not associated with the prevalence of cRORA and/or FAF GA, although eyes with NE-MNV presented smaller areas of GA.[11]

The present study represents an extension of the study conducted by the research group of Vilares-Morgado. Our primary purpose was to determine if the presence of NE-MNV influences the prevalence and progression of cRORA and the exudative conversion rate over a 2-year follow-up period in the fellow eye of patients with unilateral exudative AMD.

METHODS

This work represents a 2-year extension study of a cohort of 68 patients with unilateral exudative AMD followed in the Ophthalmology Department of Local Health Unit of São João that was previously included in a prospective study implemented in 2021, aiming to identify and quantify GA and cRORA progression, to determine the prevalence of NE-MNV and to establish its impact on atrophy growth.

Our study was approved by the Institutional Ethics Review Board of ULS São João, Porto, Portugal. The protocol conformed with the canons of the Declaration of Helsinki for research involving human participants, as well as the European Union's General Data Protection Regulation. Informed consent was waived in view of the retrospective nature of the study. This article was redacted according to the recommendations of The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.

Patients over 50 years old with unilateral exudative AMD were included. Patients with bilateral exudative AMD or with other types of retinal disorders of the study eye, patients who were unable to provide informed consent, patients with multiple previous absences in medical consultations and treatments (≥2) in the previous year, patients who were currently participating in clinical trials, and patients with poor quality retinal multimodal imaging (due to dense ocular media) were excluded. There was a loss to follow-up of 3 patients (1 patient died for other medical diseases unrelated to ocular pathology and 2 patients withdrew their consent to participate in the study). We ended up with a final sample size of 65 eyes from 65 patients.

In each study eye, we performed a complete ophthalmological examination with visual acuity (VA) determination (presented in letters measured using the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale), slit-lamp examination, intraocular pressure determination (with Goldmann applanation tonometer), and multimodal retinal imaging with color fundus photography, fundus autofluorescence (FAF), SD-OCT (spectral domain-optical coherence tomography), and OCT-A (optical coherence tomography with angiography).

All included patients underwent a study protocol of multimodal retinal imaging specifically developed for the purpose of this study, to detect the presence of NE-MNV, and GA and to measure both the area of GA and the greatest linear diameter (GLD) of cRORA.

In accordance with the "Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data",[3] NE-MNV was defined as the presence of anomalous vessels and associated tissues into the outer retina, subretinal space, or sub-RPE space without evidence of exudation (such as leakage, subretinal fluid, lipid, and subretinal hyper-reflective exudative material). Furthermore, according to the "Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3", GA was defined by the presence of well-demarcated areas of decreased signal intensity in blue-light FAF, of at least 175 μm in diameter on 30° FAF images; cRORA was defined by the presence of the following tomographic criteria: (1) a region of tomographic hypertransmission of at least 250 μm in diameter; (2) a zone of attenuation or disruption of the RPE of at least 250 μm in diameter; (3) evidence of overlying photoreceptor degeneration; and (4) the absence of scrolled RPE or other signs of an RPE tear. We have also adopted the tomographic classification criteria for incomplete RPE and outer retinal atrophy (iRORA), complete outer retinal atrophy (cORA), and incomplete outer retinal atrophy (iORA) presented in the remaining Consensus of Atrophy Meeting (CAM) reports.[13-15]

OCT-A images were obtained through dilated pupils with the SPECTRALIS Heidelberg® Retina Angiograph + OCT imaging platform (Heidelberg Engineering, Heidelberg, Germany) over 3.0×3.0-mm fields centered in the fovea with an isotropic lateral resolution of 5.7 μm/ pixel (512 A-scans × 512 B-scans). The en face avascular complex slabs of the SPECTRALIS OCT-A (after the removal of retinal vessel projection artifacts) were screened for the presence of NE-MNV, given that virtually all NE-MNV lesions present in the sub-RPE or subretinal space.[10] The presence of NE-MNV was primarily detected with OCT-A in all cases.

OCT images were obtained with the same device, over an area of 30° centered in the fovea. cRORA GLD was manually measured in OCT scans using the integrated measurement tool of the Heidelberg Eye Explorer (Heidelberg Engineering). This parameter was measured in the OCT scan with the highest horizontal/linear cRORA diameter. We used the average of three different measurements for the analysis.

Short-wave FAF images were obtained in the same visit with the same device over an area of 30° centered in the fovea (488-nm pulsed blue laser light, 500 nm barrier filter). Areas of GA were manually delineated in the FAF images with the mouse-driven cursor and the software then automatically calculates the size of the areas of interest.

OCT and OCT-A scans and FAF images were reviewed by 2 independent graders (medical retina specialists A.C. and M.F.). In case of disagreement, consensus was achieved by both readers reviewing the imaging data together again. Representative FAF, SD-OCT and OCT-A images of one case of NE-MNV without concurrent cRORA and one case of cRORA with simultaneous NE-MNV are depicted in Figs. 1 and 2.

Patients' demographic (age and gender), clinical (VA in both the study and fellow eye, ongoing treatment of the fellow eye), tomographic and angiographic (the presence of

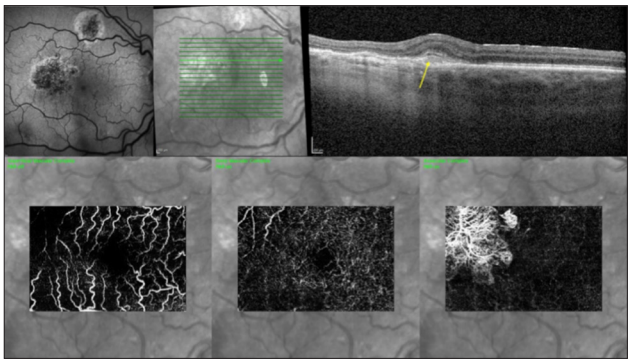


Figure 1. FAF, SD-OCT, and OCT-A images of a case of NE-MNV without concurrent cRORA. The area of NE-MNV is highlighted by a yellow arrow in the SD-OCT image, without signs of intraretinal fluid or subretinal fluid. There is no evidence of cRORA in both FAF and SD-OCT. OCT-A image includes 3 different segmentations, which correspond to the superficial vascular complex, deep vascular complex, and avascular complex slabs, as defined by the SPECTRALIS Heidelberg® Retina Angiograph (HRA) + OCT imaging platform (Heidelberg Engineering). There is evidence of a neovascular lesion in the OCT-A C-scans, in the correspondent area of the lesion in the SD-OCT.

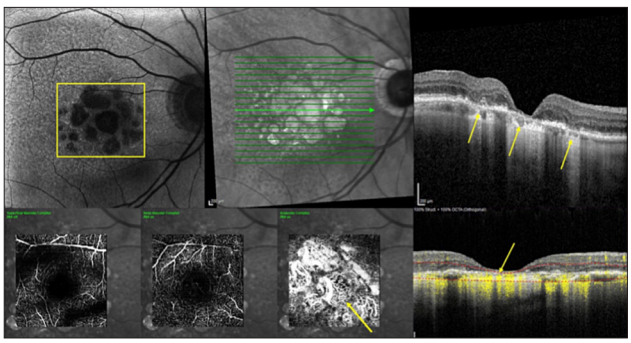


Figure 2. FAF, SD-OCT and OCT-A images of a case of simultaneous NE-MNV and cRORA. The area of cRORA is depicted within the yellow square in the FAF image and highlighted by the yellow arrows in the SD-OCT image. OCT-A image includes 3 different segmentations, which correspond to the superficial vascular complex, deep vascular complex, and avascular complex slabs, as defined by the SPECTRALIS Heidelberg® Retina Angiograph (HRA) + OCT imaging platform (Heidelberg Engineering). There is evidence of a neovascular lesion in the avascular complex slab OCT-A C-scan and corresponding increased flow in the structural OCT-B scan with flow marked in yellow (yellow arrows).

NE-MNV, the presence and GLD of cRORA in the study eye, and the type of exudative MNV in the fellow eye), and FAF data (the presence and area of GA in the study eyes) were collected from scheduled medical consultations. Geographic atrophy (GA) progression was assessed using the square root transformation of the atrophic area (√area) to reduce the dependence of growth rate on baseline lesion size and to allow for a more linear representation of atrophy enlargement over time.

Statistical analysis was performed using IBM-SPSS® for Windows®, version 27. Normally distributed data are reported as mean and standard deviation (SD), while non-normally distributed data are reported as median and interquartile range (IQR). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess whether each variable followed a normal distribution. Comparisons between baseline and the 2-year assessment regarding functional and retinal imaging characteristics of the study group were performed using the paired samples t-test. Comparisons between groups (no NE-MNV *versus* NE- MNV) were performed using the independent samples t-test (for normally distributed data) for continuous variables, while the $\chi 2$ test was used for categorical variables. In all tests, we considered statistical significance if $p<0.05$.

RESULTS

A total of 65 patients with unilateral exudative AMD of the fellow eye were evaluated over 2 years in our Ophthalmology Department.

Table 1 presents the baseline demographic and clinical characterization of our study group. The mean age was 78.02±8.167 years old (range 61-97). Mean VA in study eyes was significantly higher compared to the fellow eyes with exudative AMD (65.68±19.18 *vs* 45.29±24.37 ETDRS letters, $p<0.001$). Most fellow eyes with exudative AMD presented a type 1 neovascular membrane (53.8%), 43.1% with type 2 MNV and 3.1% with type 3 MNV, Treat-and-extend was the implemented regimen in 80% of the fellow eyes under treatment with anti-VEGF intravitreal injections (eyes with fibrosis and irreversible lesions were not receiving treatment). No study eye was receiving intravitreal therapy.

Table 1. Baseline demographic and clinical characteristics of our study group.

	N=65
Sociodemographic characteristic	61 (59)
Mean age (years)	78.02±8.167 [61-97]
Gender (female)	32 (49.2)
Clinical characteristics	
VA (ETDRS letters)	
Study eye	65.68±19.18
Fellow eye	45.29±24.37
Type of MNV of the fellow eye	
Type 1	35 (53.8)
Type 2	28 (43.1)
Type 3 (RAP)	2 (3.1)
Ongoing treatment of the fellow eye	52 (80)
Anti-VEGF treatment interval	
Every 4–6 weeks	27 (51.9)
Every 7–9 weeks	16 (30.8)
Every 10 weeks or more	9 (17.3)
Anti-VEGF drug	
Bevacizumab	28 (53.9)
Ranibizumab	2 (3.8)
Aflibercept	22 (42.3)

Values are presented as n (%) for categorical variables and as mean ± SD for continuous variables with a normal distribution. ETDRS letters, Early Treatment Diabetic Retinopathy Study visual acuity scale; anti-VEGF, anti-vascular endothelial growth factor; SD, standard deviation.

Table 2. Functional and multimodal retinal imaging characteristics of the study group, including tomographic and angiographic (SD--OCT + OCT-A) at baseline and 2-years follow-up.

N=65	Baseline	2-years	*p*-value
VA (ETDRS letters)			
Study eye	65.68±19.18	63.34±21.44	0.098
Fellow eye	45.29±24.37	42.42±28.11	0.106
MNV of the study eye, n (%)			
NE-MNV	12 (18.4)	16 (24.6)	**<0.001**
Exudative MNV	0 (0)	13 (20)	
Tomographic atrophy, n (%)			
Absent	45 (69.2)	37 (56.9)	
cRORA	12 (18.5)	13 (20)	
iRORA	3 (4.6)	2 (3.1)	**<0.001**
cORA	1 (1.5)	7 (10.8)	
iORA	4 (6.2)	5 (7.7)	
Tomographic Atrophy GLD, µm			
cRORA	1733.93±1388.6	2638.57±1967.11	**<0.001**
Range	237-4841	330-6208	
Autofluorescence characteristics			
GA area, mm^2	7.93±7.34	13.06±10.23	**<0.001**

Values are presented as n (%) for categorical variables and as mean ± SD for continuous variables. SD-OCT, spectral-domain optical coherence tomography; OCT--A, optical coherence tomography angiography; MNV, macular neovascularization; RAP, retinal angiomatous proliferation; cRORA, complete retinal pigment epithelium and outer retinal atrophy; iRORA, incomplete retinal pigment epithelium and outer retinal atrophy; cORA, complete outer retinal atrophy; iORA, incomplete outer retinal atrophy; SD, standard deviation; GLD, greatest linear diameter; GA, geographic atrophy.

Table 2 presents functional and multimodal imaging characteristics of the study group, at baseline and 2-years follow-up. At baseline there was 12 eyes with NE-MNV and overtime 4 more cases were diagnosed with NE-MNV. At the end of the study, 8 remained NE-MNV and 4 evolved to E-MNV. At the two-year mark, 13 patients had developed E-MNV; among them, 4 had a prior diagnosis of NE-MNV, while the remaining 9 had not been previously diagnosed with NE-MNV.

Regarding OCT and OCT-A evaluations in the most recent time point, we identified 16 cases of NE-MNV (accounting 4 new patients with NE-MNV compared to baseline), which corresponded to a prevalence of 24.6% in our cohort. According to OCT-A evaluation, these patients presented sub-RPE NE-MNV lesions. A total of 13 patients converted to exudative AMD in the study eye over 2 years, thus representing cases of bilateral exudative AMD. Among them, 4 (33%) had a prior diagnosis of NE-MNV. These 4 patients presented type 1 MNV and were older patients (82.25±5.8 *vs* 75.88±5.67, p=0.49)

Out of the 65 study eyes, 27 presented with tomographic signs of atrophy. cRORA was identified in 13 eyes (20%), iRORA was identified in 2 eyes, iORA was identified in 5 eyes, and cORA was identified in 7 eyes. The mean GLD of cRORA significantly increased from 1733.93 ± 1388.6 µm to 2638.57 ± 1967.11 µm during the 2 years (p<0.001). Regarding FAF characterization, GA of the study eye was identified in 13 eyes (20%), always confirmed by OCT examination. The mean area of GA significantly increased from 7.93 ± 7.34 mm^2 at baseline to 13.06 ± 10.23 mm^2 at the 2-year evaluation (p<0.001). The square root–transformed GA area increased from 2.82 ± 2.71 mm at baseline to 3.61 ± 3.20 mm at 2 years (p<0.001), corresponding to a mean enlargement of 0.79 mm over the study period. There was a significant correlation between the area of GA in the FAF and the GLD of cRORA in the OCT (r = 0.962; p<0.001) (Fig. 3).

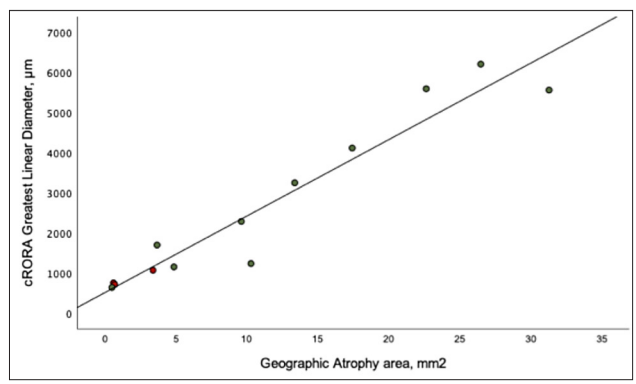


Figure 3. Scatter plot representing significant correlation between cRORA greatest linear diameter (in µm) and geographic atrophy area (in mm2) in the FAF (r = 0.889; p<0.001).

A comparison of demographic, clinical, autofluorescence, and tomographic characteristics between eyes with NE-MNV detected in OCT-A (n=16) and eyes without any evidence of NE-MNV (n=36) was performed, excluding study eyes that converted to exudative AMD during follow-up (n=13) (Table 3). Patients with evidence of NE-MNV were significantly younger when compared to the

Table 3. Comparison of demographic, clinical, autofluorescence and tomographic characteristics between groups after 2 years of follow-up, excluding patients who converted to exudative AMD (n=13).

	No NE-MNV (n=36)	NE-MNV (n=16)	*p*-value
Demographic characteristics			
Age (years)	79.31±8.9	73.06±6.54	**0.004**
Gender (female)	19 (52.8)	8 (50)	0.853
Clinical and tomographic characteristics			
VA (ETDRS letters)			
Study eye	61.91±24.38	67.88±14.54	0.142
Fellow eye	41.49±27.47	41.56±30.12	0.497
Type of MNV of the fellow eye, n (%)			0.226
Type 1	19 (52.8)	9 (60)	
Type 2	17 (47.2)	5 (33.3)	
Type 3 (RAP)	0 (0)	1 (6.7)	
Tomographic atrophy, n (%)			0.535
Absent	19 (52.8)	11 (68.8)	
cRORA	11 (30.6)	2 (12.5)	
iRORA	1 (2.8)	0 (0)	
cORA	2 (5.6)	2 (12.5)	
iORA	3 (8.3)	1 (6.3)	
Tomographic Atrophy GLD, μm			
cRORA	2629.46±2124.72	958.50±348	**0.008**
Autofluorescence characteristics			
Presence of GA	11 (30.5)	2 (12.5)	0.118
GA area, mm^2	11.93±11.08	7.58±3.84	0.186
GA progression, mm^2/year	0.44	0.53	0.125

Values are presented as n (%) for categorical variables and as mean ± SD for continuous variables. SD-OCT, spectral-domain optical coherence tomography; OCT-A, optical coherence tomography angiography; MNV, macular neovascularization; RAP, retinal angiomatous proliferation; cRORA, complete retinal pigment epithelium and outer retinal atrophy; iRORA, incomplete retinal pigment epithelium and outer retinal atrophy; cORA, complete outer retinal atrophy; iORA, incomplete outer retinal atrophy; SD, standard deviation; GLD, greatest linear diameter; GA, geographic atrophy.

group without NE-MNV (73.06±6.54 *vs* 79.31±8.9, *p*=0.004). There were no significant differences in patients' gender proportion (*p*=0.853) in both groups. VA was similar between both groups, both concerning the study (*p*=0.142) and fellow eyes (*p*=0.497).

Tomographic signs of atrophy (including cRORA, iRORA, cORA, iORA) were more frequent in eyes without NE-MNV (17 out of 36 eyes, 47.3%) compared to eyes with NE-MNV (5 out of 16 eyes, 31.3%) (*p*=0.535). cRORA was present in 11 eyes (30.6%) without NE-MNV and in 2 eyes (12.5%) with NE-MNV.

Regarding cRORA greatest linear diameter measured in OCT, eyes with NE-MNV presented a significantly smaller GLD than eyes without NE-MNV (958.50±348 *vs* 2629.46±2124.72, *p*=0.008). Eyes with NE-MNV and eyes without NE-MNV had a similar prevalence of FAF GA (2 eyes out of 16 and 12 eyes out of 36, respectively; *p*=0.118). No significant differences were found with the mean area of FAF GA between groups (*p*=0.186) nor in the GRA progression rate over the 2 years (*p*=0.125).

DISCUSSION

This work represents a 2-year extension study of a cohort of patients with unilateral exudative AMD followed in our ophthalmology department and previously included in a prospective study implemented in 2021 aiming to identify and quantify GA and cRORA progression in the study eyes of patients with unilateral exudative AMD of the fellow eye as well as to determine the prevalence of NE-MNV and its impact on atrophy growth.[11] The main findings in the current study were that, over a 2-year period of follow-up, the presence of NE-MNV was not associated with the prevalence of cRORA or FAF GA, nor with the GA progression rate per year. Nonetheless, our study confirmed the previously identified concept that NE-MNV may prevent the progression of RPE and outer retinal atrophy, as the eyes with NE-MNV presented smaller areas of GA. This work contributes to the understanding of the natural history of NE-MNV regarding its progression to exudative AMD over a short-medium term follow-up length.

Recent studies in the literature have demonstrated the existence of subclinical non-exudative macular neovascularization in the context of AMD in the fellow eyes of pa-

tients with unilateral exudative neovascular AMD, specifically with OCT-A development.[16,17] Only a few studies have evaluated the incidence of exudation in eyes with these treatment-naive NE-MNV and the association of these macular neovessels with smaller areas of cRORA.[18,19]

The study of Vilares-Morgado *et al* (2022) presented preliminary evidence of the protective feature of NE-MNV in the development and progression of RPE and outer retinal atrophy.[15] The authors identified a 14.7% prevalence of NE-MNV, and the eyes with NE-MNV (10 out of 68) presented a significantly smaller GA area than eyes without NE-MNV.

We identified a NE-MNV prevalence of 24.6% (16 out of 65). Our result is in line with the reported prevalences of NE-MNV in fellow eyes of patients with unilateral exudative AMD in a recent systematic review, ranging between 6.25% and 27%.[10]

Our study demonstrated a 33% conversion rate in 2 years in the study eyes with NE-MNV that converted to the exudative form of the disease. Cumulative incidences of exudation in patients with non-exudative MNV reported in the literature vary between 26.3% with a mean of 20 months of follow-up, 34.5% to 80% by two years.[16,20,21] These different incidences may be explained by different population characteristics such as age, the type, severity and duration of AMD in the fellow eye and by sample size in the different studies.

In our cohort, patients with NE-MNV were significantly younger than those without NE-MNV and it is crucial to acknowledge age as a potential confounding factor, given its known association with AMD development and progression. However, the approximately six-year age difference is unlikely to fully account for the observed differences in cRORA progression. There are multiple studies in the literature showing that the risk of progression of AMD is increased for each 10-year increase in age. When considering patients of the age group between 70–79 years old (which is the age range of the patients included in our cohort), there are no established differences regarding the incidence and progression rate of AMD that can be quantified by each year.[22,23] Moreover, our main analyses focused on lesion-based structural parameters rather than systemic risk factors, and the observed association between NE-MNV and smaller cRORA areas remained consistent after adjusting for baseline atrophic lesion size and follow-up duration.

While non-exudative MNV appears to be an important and acknowledged precursor for the formation of exudative neovascular AMD, there is increasing evidence suggesting a protective effect on slowing the progression of GA.

We determined a prevalence of FAF GA in the study eye of 26.2% (mean area of 13.06±10.23 mm^2, measured in FAF images) and a prevalence of tomographic cRORA of 21.5% (mean GLD of cRORA 2638.57±1967.11 μm, measured in OCT B-scans), with a significant correlation between both measurements (r=0.962; p<0.001). This result validates the use of both imaging modalities in clinical practice to evaluate the extent of progression of atrophy, as there is a strong correspondence in the atrophy measurements.[14,24]

Regarding the comparison of eyes with and without NE-MNV, there was a statistically significant difference between groups (no NE-MNV versus NE-MNV) for mean age, with the group of patients with evidence of NE-MNV being significantly younger than the group without non-exudative macular neovessels (p=0.004). Fernandes *et al* demonstrated a positive correlation between the prevalence and progression of the disease with aging.25 Higher age represents the main risk factor for AMD, as aging is associated with structural and functional changes of the retina.

There were no significant differences in patients' VA between groups, both concerning study (p=0.142) and fellow eyes (p=0.497). de Oliveira Dias *et al* described that nonexudative MNV may persist for at least 2 years without developing exudation and affecting vision, thereby confirming the subclinical feature of these lesions.16 Bailey *et al* followed 10 out of 63 eyes with NE-MNV that were asymptomatic at the time of diagnosis, and the detection of NE-MNV was not associated with any reduction in VA.[21]

Different types of exudative MNV of the fellow eyes did not seem to correlate with the prevalence of NE-MNV in our study eyes (p=0.226), despite the evidence regarding the potential beneficial nutritional support for the overlying RPE and photoreceptors.[27]

Laiginhas *et al* recently reported that the presence of NE-MNV may be considered a protective factor for the development and progression of choriocapillaris degeneration and RPE atrophy, therefore preserving foveal function by supplying oxygen to the hypoxic outer retina.[10] Vilares-Morgado *et al* conclusions support this protective feature of NE-MNV in the progression of atrophy, as the eyes with NE-MNV presented significantly smaller GA areas.[15]

The establishment of NE-MNV is associated with the presence of a RPE detachment where the non-exudative neovessels reside. The presence of these neovessels increases the sub-RPE capillary density in the involved area, as well as the sub-RPE blood flow, thus compensating for the choriocapillaris breakdown and flow deficits.[28,29] The nurturing nature of this neovascular tissue to the overlying hypoxic RPE and outer retina contributed to the existence of small and incomplete atrophic lesions that do not progress to cRORA. Moreover, the development of NE-MNV might counterbalance age-related degeneration of the Bruch's membrane, which is marked by increased calcification of elastic fibers and the buildup of extracellular deposits such as basal linear deposits and soft drusen.[30]

cRORA was present in 11 (30.6%) eyes without NE-MNV and in 2 (12.5%) eyes with NE-MNV (p=0.535). Accordingly, we found FAF GA in 11 (30.5%) eyes without NE-MNV and in 2 (12.5%) eyes with NE-MNV (p=0.118). Contrary to our hypothesis, both prevalences of cRORA and GA were similar between groups, even when considering a 2-year follow-up period. This result may be influenced by the small sample size of eyes with cRORA and by the limited follow-up period, with atrophy of the outer retina layers probably developing over longer periods.

Both mean GLD of cRORA and mean area of GA significantly increased during the 2 years (p<0.001). We found a significantly smaller cRORA greatest linear diameter measured in OCT in eyes with NE-MNV (958.50±348 μm) when compared with eyes without NE-MNV (2629.46±2124.72 μm,

p=0.008). No significant differences were found with the mean area of FAF GA between groups (*p*=0.186), although there was a non-statistically significant trend towards a lower GA area in eyes with NE-MNV (7.58±3.84 *vs* 11.93±11.08 mm^2, *p*=0.186).

Despite not proving that the presence of NE-MNV is associated with a lower cRORA and GA prevalence and a smaller GA areas, our results favor the impression that NE-MNV may be associated with smaller atrophy areas in fellow eyes of patients with unilateral exudative AMD, highlighting the protective role that these subclinical asymptomatic lesions may have in the development and enlargement of cRORA and GA, which has been already proposed and investigated by other authors. Nevertheless, the retrospective nature of this study, its cross-sectional design, single-center setting, small sample size and limited follow-up time demand caution when analyzing the results and taking definite conclusions. Further research is required to extend our knowledge on this subject with larger sample size prospective studies and randomized clinical trials regarding comprehension and management of eyes with NE-MNV.

CONCLUSION

With this work, we believe that we have contributed to understanding the natural history and behavior of NE-MNV, more specifically, regarding its progression to exudative MNV and RPE and outer retinal atrophy. Our study contributes with evidence for the protective non-exudative feature of these lesions, associated with smaller areas of RPE and outer retinal atrophy by decreasing its enlargement over time.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

AMF, RVM, RR, AC and MF: Performed the material preparation. Margarida Ferreira, Rodrigo Vilares-Morgado, Rita Rodrigues, Ângela Carneiro and Manuel Falcão.

AMF, RVM and RR: Performed data collection and analysis.

AMF, RVM and MF: Wrote the first draft of the manuscript.

All authors contributed to the study conception and design and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

AMF, RVM, RR, AC e MF: Realizaram a preparação do material. Margarida Ferreira, Rodrigo Vilares-Morgado, Rita Rodrigues, Ângela Carneiro e Manuel Falcão.

AMF, RVM e RR: Realizaram a recolha e análise dos dados.

AMF, RVM e MF: Redigiram a primeira versão do manuscrito.

Todos os autores contribuíram para a conceção e o desenho do estudo e comentaram versões anteriores do manuscrito. Todos os autores leram e aprovaram o manuscrito final.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

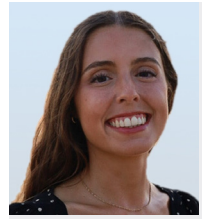
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

REFERENCES

1. Vyawahare H, Shinde P. Age-related macular degeneration: epidemiology, pathophysiology, diagnosis, and treatment. Cureus. 2022;14:e29583. doi: 10.7759/cureus.29583.
2. Deng Y, Qiao L, Du M, Qu C, Wan L, Li J, et al. Age-related macular degeneration: Epidemiology, genetics, pathophysiology, diagnosis, and targeted therapy. Genes Dis. 2022;9:62-79. doi: 10.1016/j.gendis.2021.02.009.
3. Spaide RF, Jaffe GJ, Sarraf D, Freund KB, Sadda SR, Staurenghi G, et al. Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. Ophthalmology. 2020;127:616-36. doi: 10.1016/j.ophtha.2019.11.004.
4. Green WR, McDonnell PJ, Yeo JH. Pathologic features of senile macular degeneration. Ophthalmology. 1985;92:615-27.
5. Faatz H, Rothaus K, Ziegler M, Book M, Heimes-Bussmann B, Pauleikhoff D, et al. Vascular analysis of type 1, 2, and 3 macular neovascularization in age-related macular degeneration using swept-source optical coherence tomography angiography shows new insights into differences of pathologic vasculature and may lead to a more personalized understanding. Biomedicines. 2022;10:694. doi: 10.3390/biomedicines10030694.
6. Motulsky EH, Zheng F, Shi Y, Gregori G, Rosenfeld PJ. Ana-

tomic Localization of Type 1 and Type 2 Macular Neovascularization Using Swept-Source OCT Angiography. Ophthalmic Surg Lasers Imaging Retina. 2018;49:878-86. doi: 10.3928/23258160-20181101-09.
7. Rosenfeld PJ. Optical Coherence Tomography and the Development of Antiangiogenic Therapies in Neovascular Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci. 2016;57:14-26.
8. Mehta H, Tufail A, Daien V, Lee AY, Nguyen V, Ozturk M, et al. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. Prog Retin Eye Res. 2018;65:127-46. doi: 10.1016/j.preteyeres.2017.12.002.
9. Khan H, Aziz AA, Sulahria H, Khan H, Ahmed A, Choudhry N, et al. Emerging treatment options for geographic atrophy (GA) secondary to age-related macular degeneration. Clin Ophthalmol. 2023;17:321-7. doi: 10.2147/OPTH.S367089.
10. Laiginhas R, Yang J, Rosenfeld PJ, Falcão M. Nonexudative macular neovascularization - a systematic review of prevalence, natural history, and recent insights from OCT angiography. Ophthalmol Retina. 2020;4:651-61. doi: 10.1016/j.oret.2020.02.016.
11. Vilares-Morgado R, Silva I, Cunha AM, Carneiro Â, Falcão-Reis F, Falcão M. Prevalence and Area of Retinal Pigment Epithelium and Outer Retinal Atrophy in Eyes with Non-Exudative Macular Neovascularization. Ophthalmologica. 2022;245:528-37. doi: 10.1159/000525978.
12. Sadda SR, Guymer R, Holz FG, Schmitz-Valckenberg S, Curcio CA, Bird AC, et al. Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3. Ophthalmology. 2018;125:537-48. doi: 10.1016/j.ophtha.2017.09.028.
13. Guymer RH, Rosenfeld PJ, Curcio CA, Holz FG, Staurenghi G, Freund KB, et al. Incomplete Retinal Pigment Epithelial and Outer Retinal Atrophy in Age-Related Macular Degeneration: Classification of Atrophy Meeting Report 4. Ophthalmology. 2020;127:394-409. doi: 10.1016/j.ophtha.2019.09.035.
14. Staurenghi G, Sadda S, Chakravarthy U, Spaide RF. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN•OCT consensus. Ophthalmology. 2014;121:1572-8. doi: 10.1016/j.ophtha.2014.02.023.
15. Holz FG, Sadda SR, Staurenghi G, Lindner M, Bird AC, Blodi BA, et al. Imaging Protocols in Clinical Studies in Advanced Age-Related Macular Degeneration: Recommendations from Classification of Atrophy Consensus Meetings. Ophthalmology. 2017;124:464-78. doi: 10.1016/j.ophtha.2016.12.002.
16. de Oliveira Dias JR, Zhang Q, Garcia JMB, Zheng F, Motulsky EH, Roisman L, et al. Natural History of Subclinical Neovascularization in Nonexudative Age-Related Macular Degeneration Using Swept-Source OCT Angiography. Ophthalmology. 2018;125:255-66. doi: 10.1016/j.ophtha.2017.08.030.
17. Treister AD, Nesper PL, Fayed AE, Gill MK, Mirza RG, Fawzi AA. Prevalence of Subclinical CNV and Choriocapillaris Nonperfusion in Fellow Eyes of Unilateral Exudative AMD on OCT Angiography. Transl Vis Sci Technol. 2018;7:19. doi: 10.1167/tvst.7.5.19.
18. Yanagi Y, Mohla A, Lee SY, Mathur R, Chan CM, Yeo I, et al. Incidence of Fellow Eye Involvement in Patients With Unilateral Exudative Age-Related Macular Degeneration. JAMA Ophthalmol. 2018;136:905-11. doi: 10.1001/jamaophthalmol.2018.2154.
19. Heiferman MJ, Fawzi AA. Progression of subclinical choroidal neovascularization in age-related macular degeneration. PLoS One. 2019;14:e0217805. doi: 10.1371/journal.pone.0217805.
20. Capuano V, Miere A, Querques L, Sacconi R, Carnevali A, Amoroso F, et al. Treatment-Naïve Quiescent Choroidal Neovascularization in Geographic Atrophy Secondary to Nonexudative Age-Related Macular Degeneration. Am J Ophthalmol. 2017;182:45-55. doi: 10.1016/j.ajo.2017.07.009.
21. Bailey ST, Thaware O, Wang J, Hagag AM, Zhang X, Flaxel CJ, et al. Detection of Nonexudative Choroidal Neovascularization and Progression to Exudative Choroidal Neovascularization Using OCT Angiography. Ophthalmol Retina. 2019;3:629-36. doi: 10.1016/j.oret.2019.03.008.
22. Korb CA, Elbaz H, Schuster AK, Nickels S, Ponto KA, Schulz A et al. Five-year cumulative incidence and progression of age-related macular degeneration: results from the German population-based Gutenberg Health Study (GHS). Graefes Arch Clin Exp Ophthalmol. 2022;260:55-64. doi: 10.1007/s00417-021-05312-y.
23. Farinha CVL, Cachulo ML, Alves D, Pires I, Marques JP, Barreto P et al. Incidence of Age-Related Macular Degeneration in the Central Region of Portugal: The Coimbra Eye Study - Report 5. Ophthalmic Res. 2019;61:226-35. doi: 10.1159/000496393.
24. Ehlers JP, McConville C, Yordi S, Cetin H, Cakir Y, Kalra G, et al. Correlation Between Blue Fundus Autofluorescence and SD-OCT Measurements of Geographic Atrophy in Dry Age-Related Macular Degeneration. Am J Ophthalmol. 2024;266:92-101. doi: 10.1016/j.ajo.2024.04.031.
25. Fernandes AR, Zielińska A, Sanchez-Lopez E, Dos Santos T, Garcia ML, Silva AM, et al. Exudative versus Nonexudative Age-Related Macular Degeneration: Physiopathology and Treatment Options. Int J Mol Sci. 2022;23:2592. doi: 10.3390/ijms23052592.
26. Heesterbeek TJ, Lorés-Motta L, Hoyng CB, Lechanteur YT, den Hollander AI. Risk factors for progression of age-related macular degeneration. Ophthalmic Physiol Opt. 2020;40:140-70. doi: 10.1111/opo.12675.
27. Yang J, Zhang Q, Motulsky EH, Thulliez M, Shi Y, Lyu C, et al. Two-Year Risk of Exudation in Eyes with Nonexudative Age-Related Macular Degeneration and Subclinical Neovascularization Detected with Swept Source Optical Coherence Tomography Angiography. Am J Ophthalmol. 2019;208:1-11. doi: 10.1016/j.ajo.2019.06.017.
28. Sohn EH, Flamme-Wiese MJ, Whitmore SS, Workalemahu G, Marneros AG, Boese EA, et al. Choriocapillaris Degeneration in Geographic Atrophy. Am J Pathol. 2019;189:1473-80. doi: 10.1016/j.ajpath.2019.04.005.
29. Nassisi M, Shi Y, Fan W, Borrelli E, Uji A, Ip MS, et al. Choriocapillaris impairment around the atrophic lesions in patients with geographic atrophy: a swept-source optical coherence tomography angiography study. Br J Ophthalmol. 2019;103:911-7. doi: 10.1136/bjophthalmol-2018-312643.
30. Curcio CA. Antecedents of Soft Drusen, the Specific Deposits of Age-Related Macular Degeneration, in the Biology of Human Macula. Invest Ophthalmol Vis Sci. 2018;59:Amd182-amd94. doi: 10.1167/iovs.18-24883.



Corresponding Author/
Autor Correspondente:

Ana Margarida Ferreira
Department of Ophthalmology
of São João Hospital,
Avenida Prof. Hernâni Monteiro,
4202-451 Porto, Portugal
E-mail: amargaridapferreira@gmail.com

ORCID: 0009-0000-3592-2820