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VALIDATION OF THE RECENTLY DEVELOPED ATN CLASSIFICATION AND GRADING SYSTEM FOR MYOPIC MACULOPATHY

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Purpose: To validate the recently developed ATN grading system for myopic maculopathy to classify eyes with pathologic myopia.

Methods: Cross-sectional study. A series of consecutive eyes diagnosed with pathologic myopia and signs of myopic maculopathy (grade ≥1 for atrophic, tractional, or neovascular components of the ATN), with a refractive error > −6.0 diopters (D), were included. All patients underwent complete ophthalmological examination including fundus photography and swept-source optical coherence tomography. Six observers graded each eye twice using the ATN system (≥15 days between assessments) based only on the aforementioned data.

Results: Sixty eyes from 47 patients (61.7% female) were graded. Mean patient age was 63.2 ± 11.7 years. The mean spherical equivalent was −13.8 ± 6.5 D. Mean axial length was 28.6 ± 2.16 mm. Overall, the mean intraobserver agreement (%) for the same image was 92.0%, and the mean interobserver agreement for the second image was 77.5%. The weighted Fleiss k showed excellent correlation (k > 0.8) for the traction and neovascularization components and good correlation (0.75) for atrophy. Interobserver agreement for each of these three components was 95.2%, 98.4%, 95.0%, respectively.

Conclusion: Application of the ATN resulted in high intraobserver and interobserver correlation, underscoring the reproducibility of the system.

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Myopia is a common and increasingly prevalent ocular disorder affecting 1.6 billion people worldwide. By the year 2020, approximately 2.5 billion people are expected to have myopia, and up to one-third of these patients will have high myopia. The highest reported prevalence rates are in East Asia, where myopia affects 6.8% to 21.6% of the population.[1]

High myopia is defined as an axial length ≥26.0 to 26.5 mm and/or a spherical equivalent > −6.0 diopters (D).[2–4] Pathologic myopia (PM) has been defined as structural changes in the eye leading to vision loss in patients with high myopia,[5–7] with posterior staphyloma and axial elongation playing an important role in the changes leading to vision loss.[1,8–11]

Pathologic myopia-related complications are the leading cause of blindness in East Asia.[10,12–14] A study conducted in Japan found that 12.2% of patients with severe vision loss[15] have PM. Another study estimated that up to 6.7 million people in China have severe vision loss associated with PM. In Europe, PM is estimated to cause up to 7.8% of cases of blindness.[16–19]

A new classification and grading system was recently developed to provide clinicians with a more reliable and more comprehensive approach to grading myopic maculopathy (MM) than previously available systems.[1] This new system, known as the ATN grading and classification system, is based on the grade of three variables: atrophy (A), traction (T), and neovascularization (N). Current classification systems for atrophic MM[20] do not account for traction- and neovascularization-related alterations, both of which are highly relevant to MM. However, given the relatively recent introduction of the ATN system, more data are needed to verify its reliability and reproducibility.

In this context, the main aim of the current study was to validate the ATN system by determining the intraoberver and interobserver agreement among six retinal specialists in grading and classifying a series of eyes diagnosed with MM.

Patients and Methods

This was a retrospective review of medical records in a series of 60 consecutive eyes previously diagnosed with PM at the Puerta de Hierro-Majadahonda University Hospital (Madrid, Spain). To evaluate the interobserver and intraobserver reliability and reproducibility of the recently proposed ATN classification and grading system,[1] six international retinal specialists graded all eyes according to the ATN criteria. These grades were then compared to determine the interobserver and intraobserver agreement.

Inclusion criteria were as follows: eyes with a refractive error > -6.0 D with $\geq$ Grade 1 on any of the three components (atrophy, traction, or neovascularization) of the ATN classification scale were consecutively included. Fundus photography and swept-source optical coherence tomography (Triton, Topcon, Co, Tokyo, Japan) were performed in all patients.

A senior retinal specialist (J.M.R.-M.), two retinal specialists involved in the development of the ATN classification system (J.R.-M. and I.F.M.), and three external, international retinal specialists (K.O.-M, C.M.G.C., and R.S.) all graded the same patients twice according to the ATN criteria (Table 1) based on fundus photography and vertical and horizontal 12-mm, fovea-centered swept-source optical coherence tomography B-scans. No other clinical data were used to classify these eyes. Each specialist graded the eyes twice with a $\geq$15-day interval between assessments. To ensure objectivity, no identifying data were available to the specialists during the grading process.

This research study adhered to the tenets of the Declaration of Helsinki. The retrospective review of patient records was approved by the Ethics Committee at our institution.

Table 1. ATN Classification System

Atrophic Component (A)	Tractional Component (T)	Neovascular Component (N)
A0: No myopic retinal lesions	T0: No macular schisis	N0: No myopic CNV
A1: Tessellated fundus only	T1: Inner or outer foveoschisis	N1: Lacquer cracks
A2: Diffuse chorioretinal atrophy	T2: Inner + outer foveoschisis	N2a: Active CNV
A3: Patchy chorioretinal atrophy	T3: Foveal detachment	N2s: Scar/Fuchs spot
A4: Complete macular atrophy	T4: Full-thickness MH	
	T5: MH + retinal detachment	

From Ruiz-Medrano J. Prog Retin Eye Res. 2019; 69:80 to 115.
MH, macular hole.

Table 2. Intragrader Agreement

Variable	Observer	% Agreement	k*	SE
Atrophic component	1	85.0	0.779	0.068
	2	91.7	0.876	0.053
	3	96.7	0.950	0.035
	4	93.3	0.950	0.035
	5	78.3	0.665	0.079
	6	91.5	0.878	0.051
	Total	89.2	0.857	0.023
Traction component	1	96.7	0.931	0.047
	2	96.7	0.938	0.043
	3	100	1.000	0.000
	4	93.3	0.917	0.057
	5	88.3	0.748	0.084
	6	93.2	0.835	0.078
	Total	94.4	0.901	0.023
Neovascular component	1	91.7	0.841	0.064
	2	98.3	0.964	0.035
	3	98.3	0.963	0.037
	4	83.3	0.835	0.069
	5	86.7	0.766	0.076
	6	98.3	0.962	0.037
	Total	92.5	0.884	0.024

*Weighted Kappa statistic.

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Table 3. Intergrader Agreement

Variable	% Intergrader Agreement	k	95% CI
Unweighted			
Fleiss kappa			
Atrophic	95.2	0.753	0.664–0.841
Traction	98.4	0.847	0.730–0.964
Neovascular	95.0	0.849	0.767–0.931
Weighted			
Fleiss kappa			
Atrophic	95.2	0.753	0.664–0.841
Traction	98.4	0.847	0.730–0.964
Neovascular	95.0	0.849	0.767–0.931

CI, confidence interval.

Statistical Analysis

Intraobserver agreement, defined as the percentage agreement between the two assessments made by the same observer for each eye, and weighted kappa statistics were calculated. Interobserver agreement (defined as the percentage agreement among the six observers with regards to the grade made on the second assessment for each eye), Fleiss kappa statistics, and weighted Fleiss kappa statistics were then obtained. The kappa statistic (k) was considered moderate ($k > 0.4$), good ($k > 0.6$), or excellent ($k > 0.8$).

Results

A total of 60 eyes (30 right and 30 left eyes) from 47 patients (29 women, 61.7%) were graded. In all eyes, at least one of the three components (A, T, N) was Stage 1 or higher. The mean patient age was 63.2 ± 11.7 years (range, 43–95). The mean spherical equivalent was −13.8 ± 6.5 D (range, −6.0 to −26.0). The mean axial length was 28.6 ± 2.16 mm (range, 26–32.6).

The mean intraobserver agreement and weighted k values for the 60 images are shown in Table 2. As that table shows, the mean overall intraobserver agreement (%) for all observers grading the same image twice was 92.0%. The mean intraobserver agreement for each component (A, T, N) was 89.2%, 94.4%, and 92.5%, respectively. For the T and N components, the weighted k value was excellent ($k > 0.8$) for five of the observers and good ($k > 0.74$) for the sixth observer. The k value for the atrophy component was good ($k > 0.6$) for two observers and excellent for the other four observers.

The mean interobserver agreement (%) for the second image among the six graders was 77.5% (Table 3). Interobserver agreement was analyzed by component, finding agreements of 67.3% (atrophy), 84.9% (traction), and 80.4% (neovascularization). To improve the statistical analysis, quadratic weight for disagreement was calculated with a weighted Fleiss $k > 0.8$ (excellent) for the T and N components and $k = 0.75$ (good) for atrophy. The interobserver agreement for the A, T, and N components once weighted was, respectively, 95.2%, 98.4%, and 95.0%.

Figures 1 and 2 provide an example of the classification of two different eyes. Figure 1 depicts an eye with patchy atrophy, outer foveoschisis, and no signs of choroidal neovascularization (CNV), which was classified as stage A3T1N0. Figure 2 shows a highly myopic eye with geographic atrophy, outer and inner foveoschisis, and scarring from an old, inactive CNV, which was classified as stage A4T2N2s.

The interrater agreement for all variables is shown in Table 4. The weakest levels of agreement were observed for the atrophic component, particularly Stage A1 (agreement: 0.42) and Stage A2 (0.47). Intergrader agreement was better for Stages A3 and A4 (Table 4); however, the A4 data were excluded from the statistical analysis due to the small number of cases ($n = 3$). Agreement for the tractional and neovascular components was good or excellent, ranging from $k = 0.628$ to $k = 0.854$, except for stage N1, which was also excluded from the analysis due to the small number of cases (Table 4). The intergrader agreement was either good or excellent ($k = 0.8$) for both T3 and T4.

Discussion

In this study, we sought to determine the reliability and reproducibility of the newly introduced ATN

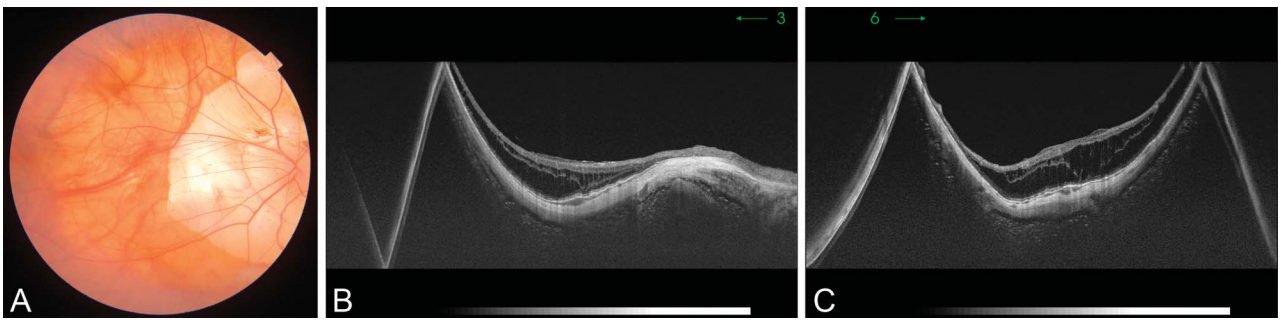

Fig. 1. Highly myopic eye with patchy atrophy, outer foveoschisis, and no signs of CNV would be classified as A3T1N0.

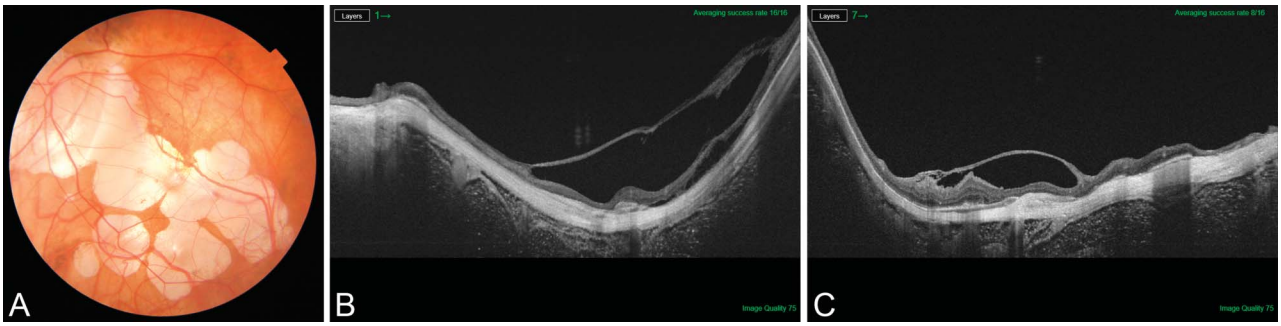

Fig. 2. Highly myopic eye with geographic atrophy, outer and inner foveoschisis, and scar from old, inactive CNV would be classified as A4T2N2s.

grading and classification system for MM. Overall, the mean intraobserver agreement for the same image was high (92.0%), with intraobserver agreement rates of 89.2%, 94.4%, and 92.5%, respectively, for the atrophic, tractional, and neovascular components. With regards to the interobserver findings, agreement for the second image was 77.5%. By component, the percentage interobserver agreement was 67.3% (atrophy), 84.9% (traction), and 80.4% (neovascularization). The interobserver agreement for each of these three components was 95.2%, 98.4%, 95.0%, respectively. These findings confirm the validity and reproducibility of the ATN classification system in eyes with MM.

As the results shown in Tables 2 and 3 make clear, the interrater agreement (k) was excellent ($k < 0.8$), ranging from 92.5% to 98.4% for the T and N variables. Although agreement for variable A was also good, $k = 0.753$, with 95.2% agreement, it is clear that this result could be further improved. In this regard, this study reveals the difficulty of differentiating between Stages A1 and A2, especially in less pigmented eyes. Given the slow clinical migration from Stage A1 to Stage A2, and considering that this change in staging has no functional repercussions, it might be better to combine these two stages (A1 and A2) into a single stage in the ATN system. These two categories are difficult to separate on color fundus photographs, and immediate correlation with vision would support this unification. However, the data reported by Ohno-Matsui et al suggest that "diffuse atrophy" is accompanied by choroidal thinning (a feature that was not considered in the ATN classification). Consequently, eyes with diffuse atrophy may have a different long-term prognosis. The relevant change in the course of the disease occurs when a patient develops atrophic patches, which suggests that diffuse, patchy, and complete atrophy should be used to define the atrophic component of the classification, thus simplifying this aspect. Full-thickness macular holes and macular holes with retinal detachment are simple, straightforward cases to diagnose, which would explain the strong overall agreement among the six graders. Regarding the neovascular component, results were certainly good, although a higher agreement could have been expected. Changes occurring in the highly myopic fundus such as retinal pigment epithelium remodeling make the diagnosis of CNV challenging in some cases. Authors of the ATN classification agreed to define the neovascular component as the presence of a Type 2 CNV on optical coherence tomography images. With respect to the difference between active and scar lesions, neovascular activity was again optical coherence tomography based and was defined as Type 2 CNV that showed any intraretinal/subretinal fluid and/or blurred boundaries/external limiting membrane.[7,21]

The tumor, nodes and metastases (TNM) cancer staging system[22] stands out as a simple yet comprehensive, practical method of staging cancer. Similarly, the ATN classification system seeks to replicate this highly successfully staging system by including the three main components of MM—atrophy, traction,

Table 4. Intergrader Agreement

	n	k
Variable atrophic		
1	10	0.421
2	30	0.479
3	17	0.627
4	3	0.685
Variable traction		
0	42	0.732
1	9	0.767
2	7	0.813
3	1	0.830
4	1	0.854
Variable neovascular		
0	39	0.757
1	2	0.108
2a	8	0.674
2s	11	0.628

Fleiss kappa statistic.

Table 5. Myopic Foveoschisis Classification

S0	Absent
S1	Extrafoveal
S2	Foveal only
S3	Foveal but not entire macula
S4	Entire macula

Shimada et al. Am J Ophthalmol 2013.

and neovascularization—together with three letters to further subclassify this pathology. Although other current classification systems classify foveoschisis extension (Table 5),[23] foveoschisis layers involved (Table 6),[17,20] or atrophy (Table 7),[20] these approaches may understage the true clinical status of some patients (Figures 1 and 2). By contrast, the ATN system integrates three key components (A, T, and N) with the corresponding numerical grade, allowing clinicians to classify highly myopic eyes in a simple, complete, and systematic manner that is both easy to apply and understand. Importantly, this proposed classification system does not alter the current atrophy classification but rather provides a new way of classifying the tractional and neovascular components (Table 1).

The availability of a precise, simple staging system for MM would permit better follow-up and help to unify the reporting of clinical findings for future research. In addition, the use of the ATN to evaluate the clinical course of the patient over time would provide invaluable information about the natural history of the disease.[1]

Study Strengths and Limitations

The main limitations of this study are the small number of cases (60 eyes) and the limited number of cases at certain stages (e.g., Stages A4, T3, T4, and N1; Figure 1), which was related to the study design (the cases were included consecutively, provided they met the study inclusion criteria, to obtain a sample that was representative of actual clinical practice). Another limitation was the exclusion of dome-shaped macula from the ATN classification system. By contrast, the main strengths of the study are the relatively large number (n = 6) of observers (including three independent international observers from three different countries), the excellent concordance levels obtained for both intragrader and intergrader agreement, and the consecutive selection of the patients from real clinical practice in a tertiary care hospital.

Table 6. Foveoschisis Layer Classification

	Inner	Outer	Inner + Outer
Involved layers	IPL + GCL + RNFL	OPL + ONL	IPL + GCL + RNFL + OPL + ONL

GCL, ganglion cell layer; IPL, inner plexiform layer; OPL, outer plexiform layer; RNFL, retinal fiber layer.

Table 7. Myopic Atrophy Classification

	Atrophy Degree	"Plus" Signs
0	No myopic retinal lesions	Lacquer cracks
1	Tessellated fundus only	Fuchs spot
2	Diffuse chorioretinal atrophy	Myopic CNV
3	Patchy chorioretinal atrophy	
4	Macular atrophy	

Conclusion

The results of this study validate the reliability of the recently proposed ATN classification system for MM. The results of this study show that the system has a high intraobserver and interobserver correlation, suggesting that the system is reliable and highly reproducible.

This new grading and classification system is simple yet comprehensive, taking into account the three main components (atrophy, traction, and neovascularization) of the disease. If this system becomes widely adopted for the classification of PM, it will allow for simpler, more accurate comparisons of findings from clinical trials and epidemiologic studies. However, further studies with larger sample sizes, more observers, and a wider representation of all disease stages will be necessary to confirm the validity of this system. The proposed modifications to the original ATN classification should also be tested to determine whether they further improve this system.

Key words: myopic maculopathy, myopic traction maculopathy, myopic choroidal neovascularization, myopic atrophy, ATN classification.

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