

# Intra and Inter-observer Concordance of a New Classification System for Myopic Maculopathy

Rong-rong Zhang

First Affiliated Hospital of Wannan Medical College

Yan Yu

First Affiliated Hospital of Wannan Medical College

Yin-fen Hou

First Affiliated Hospital of Wannan Medical College

Chang-fan Wu (✉ [wucangfan@sina.com](mailto:wucangfan@sina.com))

Department of Ophthalmology, Yijishan Hospital of Wannan Medical College, Wuhu 241001, Anhui Province, China.

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## Research Article

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## Abstract

**Background:** Myopic maculopathy (MM) is one of the major causes of visual impairment and irreversible blindness in eyes with PM. However, the classification of each type of lesion associated with MM has not been determined. Recently, a new MM classification system was proposed, known as the ATN grading and classification system, which was based on the fundus photographs and OCT images, including three variable components: atrophy (A), traction (T), and neovascularization (N). Hence, this study aimed to perform an independent interobserver and intraobserver agreement evaluation of the recently developed ATN grading system for MM.

**Methods:** This was a retrospective study. Fundus photographs and the optical coherence tomography (OCT) images of 125 patients (226 eyes) with various of MM were evaluated and classified using the ATN grading of the new MM classification system by four evaluators (2 attending ophthalmologists and 2 ophthalmic residents). All cases were repeatedly evaluated by the same evaluators after an interval of 6 weeks. The Kappa coefficient ( $\kappa$ ) and 95% confidence interval (CI) were used to determine the interobserver and intraobserver agreement.

**Results:** The interobserver reliability was substantial when considering the maculopathy type (A, T, and N). The weighted Fleiss  $\kappa$  values for each MM type (A, T, and N) were 0.651 (95% CI: 0.602–0.700), 0.734 (95% CI: 0.689–0.779), and 0.702 (95% CI: 0.649–0.755), respectively. The interobserver agreement when considering the sub-types was good or excellent, except for stages A1, A2, and N1 which weighted  $\kappa$  value was less than 0.6, with a moderate agreement. The intraobserver reproducibility of types or sub-types was excellent, with  $\kappa>0.8$ . No significant differences were observed between attending ophthalmologists and residents in the interobserver reliability and intraobserver reproducibility.

**Conclusions:** The ATN classification allows an adequate agreement among ophthalmologists with different qualifications and by the same observer on separate occasions. Future prospective studies should further evaluate whether this classification can be better implemented at clinical decision-making and disease progression assessment.

## Background

Myopia has been one of the global public health problems leading to visual impairment and blinding complications, especially in East Asia [1]. By the year 2050, approximately 4.76 billion people (49.8%) are called upon to have myopia, and up to 938 million people (19.7%) will have high myopia (HM) [2]. The prevalence of pathologic myopia (PM) is released to be 0.9–3.1%, which is a leading cause of irreversible visual impairment in East Asia [3-5].

Myopic maculopathy (MM) as one of the major causes of visual impairment and irreversible blindness in eyes with PM that is predicted to impact approximately 55.7 million people and up to 18.5 million people worldwide in 2050, respectively [6-7]. Although the clinical importance of MM, the classification of each type lesion associated with MM has not been determined and the current classification systems for MM

cannot entirely explain the various changes that occur in the patient's macula. In 2015, an international panel of researchers in myopia established a grading system for MM called the META-PM classification, based on color fundus photography [8]. But, other myopic macular lesions such as myopic traction maculopathy (MTM) and dome shaped macula (DSM) were not included in the META-PM classification because they only apply fundus photographs [9-10]. In addition, fundus images may look different due to the background pigmentation among ethnic groups and the use of different examinations, which could affect an reliable diagnosis of fundus lesions. So, it is important to establish whether OCT image can be used as an objective method to identify and classify MM. Considering the shortcomings of the META-PM system and the convenience of the OCT technology, a new MM classification system was proposed, known as the ATN grading and classification system, which includes three variable components: atrophy (A), traction (T), and neovascularization (N) [11]. This new grading system with a efficient and comprehensive approach, relating fundus photographs and OCT images, to a more precise definition of disease stages and grading management, and further to provide great value for early prevention of disease, selection of surgical methods and evaluation of prognosis.

Although many studies have analyzed the risk factors and progressive pattern of MM based on META-PM, no research has been conducted within the same HM population to comprehensively analyze the development pattern of the MM based on the new MM grading system. And the agreement analysis to validate the ATN classification system was just performed by retinal specialists. So, the aim of the present study was to perform an independent inter- and intra-observer agreement to validate the ATN grading and classification system among two different levels of the evaluator during grading and classifying the fundus lesions which diagnosed with MM.

## Methods

### Study population

This retrospective study collected 125 patients (226 eyes) with HM who underwent fundus photographs and OCT examinations at our Hospital, including 62 males and 63 females. To perform an adequate agreement study, patients with all types of retinal and choroidal lesions as defined by the recently proposed ATN classification system were included. The inclusion criteria included refractive error  $\leq -6.0\text{D}$  or axial length  $\geq 26.0\text{mm}$  with the atrophy degree equal or more than grade 1 on the three components (atrophy, traction, or neovascularization) of the ATN classification. And the exclusion criteria were other retinal or choroidal disorders, such as diabetic retinopathy; retinal vascular diseases, including retinal vein occlusions and age-related macular degeneration; poor quality of fundus and OCT images; and a history of vitreoretinal surgery.

### Ophthalmic examinations

Comprehensive ophthalmologic examinations were performed in all participants. An autorefractometer (Topcon Corp, Tokyo, Japan) was used for spherical equivalent refraction measurements, and axial length was recorded using the IOLMaster (Carl Zeiss Meditec, Jena, Germany). A dilated 45°digital color

fundus photographs (centered on the macular) were taken using a TRC-50DX (Topcon Corp, Tokyo, Japan). Vertical and horizontal scans that passed through the center of the fovea and raster scans covering all the macular complications were acquired using the spectral domain OCT (Heidelberg Engineering, Heidelberg, Germany).

## Evaluation criteria

The evaluators were four ophthalmologists representing two different levels of training in MM: two fellowship-trained ophthalmologists with experience in MM and two ophthalmic residents. All the evaluators were trained in this new classification system (S.figure) before performing the assessment, and they were provided with the original article by Ruiz-Medrano et al.[11] to solve any uncertainty at the time of evaluation. Each evaluator graded the fundus and OCT images twice with a 6-week interval between assessments. This study adhered to the principles of the Declaration of Helsinki, and the retrospective review of patient records was approved by the Ethics Committee of Wannan Medical College Yijishan Hospital (2019A052).

## Statistical analysis

Statistical analysis was conducted using SPSS for windows version 22.0 (SPSS, Inc., Chicago, IL). Interobserver agreement was achieved by comparing the initial responses of all evaluators. Intraobserver agreement was determined by comparing the responses of the same evaluator between two assessments of the same cases, which were presented in a random sequence after an interval of 6 weeks. The kappa coefficient ( $\kappa$ ) was used to identify inter- and intra-observer agreement. The agreement was initially evaluated at the main-type level (A, T and N) and then at the sub-type level for A, T and N lesions. Levels of agreement for  $\kappa$  were described by Landis and Koch [12], with  $\kappa$  values 0.00–0.20 considered slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement, and 0.81–1.00, almost excellent agreement.

# Results

## Demographic and clinical characteristics

A total of 125 consecutive patients with HM were collected, and the fundus photographs and OCT images of 226 eyes were assessed and graded by two different levels of evaluator. Among all eyes, any of the three components (A, T and N) was stage 0 or higher except component A (stage  $\geq 1$ ). The average age of the patient was  $56.53 \pm 16.76$  years with a range of 18 to 94 years. The mean spherical equivalent was  $-12.6 \pm 4.5$  D with a range of -6.0 to -24.0 D and the mean axial length was  $29.4 \pm 3.08$  mm with a range of 26.0 to 35.2 mm.

## Interobserver Reliability

The total interobserver agreement was shown in table 1, finding the weighted Fleiss  $\kappa$  values for each MM type (A, T, and N) were 0.651 (95% CI: 0.602–0.700), 0.734 (95% CI: 0.689–0.779), and 0.702 (95% CI:

0.649–0.755), respectively. These values were considered substantial agreement for type A, T and N lesions. Although there were no significant differences between attending surgeons and residents in the specific grading agreement of A, T, and N type lesions, the weighted  $\kappa$  values of residents were lower than those in attending surgeons (Table 2). Agreement for each sub-type was good or excellent, ranging from  $\kappa = 0.662$  to  $\kappa = 0.835$ , except for stages A1, A2, and N1 which weighted  $\kappa$  value was less than 0.6, with a moderate agreement (Table 3).

### **Intraobserver Reproducibility**

The intraobserver agreement and weighted  $\kappa$  values for the 226 images were shown in table 2 and 3. In the repeated evaluation six weeks after the first assessment, we did not observe significant differences in the intraobserver agreement of specific A, T and N type lesions between attending surgeons and residents. When we evaluated the level of agreement according to the subtype level, the intraobserver agreement was excellent ( $\kappa > 0.8$ ). The detailed intraobserver agreement by sub-type level was shown in table 3.

### **Illustrate with examples**

Figures 1 and 2 present an example of the classification of two different eyes. Figure 1 depicts an eye with patchy atrophy, foveal detachment, and no signs of choroidal neovascularization (CNV), which was classified as stage A3T3N0 both in ophthalmologists with different qualifications. Figure 2 shows a highly myopic eye with tessellated fundus, inner foveoschisis, and macular lacquer cracks (black arrow), which was classified as stage A1T1N1 by attending ophthalmologists, while classified as stage A1T1N0 by ophthalmic residents.

## **Discussion**

In this study, we performed an independent inter- and intra-observer agreement assessment of the ATN grading and classification system for MM. The full inter-observer agreement in our study was substantial for each MM type (A, T, and N), and the intra-observer agreement was excellent. In addition, half of our evaluators were residents, and even though their agreement was not significantly different from that of fellowship-trained attending ophthalmologists, the ophthalmic residents exhibited  $\kappa$  values considered as moderate or substantial agreement less than attending ophthalmologists, who had higher  $\kappa$  values considered as substantial or excellent agreement. These results upheld the validity and reproducibility of the recently proposed ATN classification system in the eyes of MM.

In our study, the results showed that the level of inter-observer agreement was slightly lower in atrophic component compared with other components among attending ophthalmologists and ophthalmic residents, which might be influenced by A1 and A2 grading. This finding was consistent with the agreement reported by the authors who developed this classification [13], but the level of inter-observer agreement in our study was just slightly lower than that in their study (A:  $\kappa = 0.753$ ; T:  $\kappa = 0.847$ ; N:  $\kappa = 0.849$ ). The possible reason for this outcome could be the small sample (60 eyes) analysis and the

retinal specialists involvement. When analysis of the inter-observer agreement at the sub-type level of each type, we could be found that the  $\kappa$  value at stages A1, A2 and N1 was considered moderate agreement, while other sub-type was substantial or excellent . This outcome was similar to the recently reported data from the study by Ruiz-Medrano et al. [13], which verified that the disease migration from stage A1 to stage A2 was slow and only through color fundus photographs to differentiate these two categories was difficult. Therefore, they proposed that combining these two stages (A1 and A2) into a single stage in the ATN classification system was better. However, early researchon the long-term development pattern of MM have found that the initial sign of highly myopic eye had progressed to the MM stage was the occurrence of a tessellated fundus which can developed to diffuse atrophy, lacquer cracks, or more typically to the formation of a CNV with time [14]. In addition, the clinical characteristics of these two categories were also different, patients with tessellated fundus were young and had significantly better visual acuity, while patients who developed diffuse chorioretinal atrophy were generally over 40 years old with poor vision [15]. Therefore, we believe that it is reasonable for the ATN system to classify the tessellated fundus and diffuse chorioretinal atrophy into two grades, considering the pathological features and progression trend of these two categories based on the earlier studies. At present, the key to determining these two categories was to identify relatively objective quantitative indicators, rather than only limited to the color changes in fundus photographs. Fang et al. [16] has reported that the choroidal thickness (CT) was dramatically diminished from the tessellation to peripapillary diffuse choroidal atrophy (PDCA) only in the nasal location, and the cut-off value of CT to evaluate the eyes with PDCA from tessellation was 56.5 um nasal to the fovea, which was useful in differentiating these two categories. Therefore, cut-off CT value can be used as a supplemental method in combination with fundus photography for accurate diagnosis of the tessellated fundus and diffuse chorioretinal atrophy lesions.

The present study also found that the inter-observer agreement for the N1 level was moderate, speculating the possible reason might be due to the absence of uniform diagnostic criteria and the different observation index of two diagnostic tools. Lacquer cracks (LCs) in fundus were shown irregular, yellowish linear lesions often branching and crisscrossing in the macula, while OCT showed discontinuities of retinal pigment epithelium [17]. The evaluator took different types of images and standard grading N1 that led to some deviation in the results. In addition, previous studies have claimed that LCs were risk factors for CNV [14, 18-19], but the progression of LCs into CNV does not appear common (13%), most LCs developed to patchy atrophy (43%) [14]. And the research of posterior fundus changes in PM also found that LCs often appeared at the early stage of MM, and the young individuals often do not have noticeable staphyloma or early atrophic changes of the retina [20]. However, the ATN system classified LCs into the neovascular group, which may lead to the classification of someLCs that may develop into patchy atrophy as the neovascular lesion and further impact the validity of this classification system in a long-term progress observation [21]. Consequently, further study to determine the standard of LCs identification and modification of LCs classification was necessary and important.

The main limitations of this study are the limited number of samples at certain stages (such as stages T3, T4, and N1) and the limited OCT images (just centered on the macula), which relatively affected the

study results. In some cases, the appearance of the three components in fundus photographs and OCT images may exist interact affection. When fundus occurred macular hemorrhage, the T lesion may be affected and frequently misdiagnosed as foveal detachment (T3), and the macular holes with retinal detachment (T5) lesion often affected the fundus photographs quality that leads to grade A stage was difficult to identified. Chen and colleagues[21] in the research of the morphological characteristics and risk factors of MM proposed that the coexistence of the three components could influence the correlation between risk factors and specific type of MM. Therefore, dissolving the impact of coexistence among the three components, whether in acccurative diagnosis or observation of the progression of MM was still a challenge. On the contrary, the strengths of this study design included substantially large sample sizes and the participation of observers with different qualifications.

## Conclusion

In conclusion, this study validates the reliability of the recently proposed ATN classification system with a relatively high interobserver and intraobserver agreement among ophthalmologists with different qualifications. The ATN classification system includes three main components (atrophy, traction, and neovascularization) of the fundus lesions, which can be comprehensive and efficient comparisons of findings from clinical trials and epidemiologic studies, improving the diagnosis and grading management of MM, and providing greater values for the research of MM progress and intervention. However, the further modifications to the original ATN classification should be tested to improve the deficiencies in clinical application, and the prospective studies with larger sample sizes in investigate the progression pattern of MM based on the ATN classification system will be necessary to further confirm the validation of this classification system.

## Abbreviations

MM: Myopic maculopathy; A: Atrophy; T: Traction; N: Neovascularization; OCT: Optical coherence tomography;  $\kappa$ : Kappa coefficient; CI: Confidence interval; HM: High myopia; PM: Pathologic myopia; MTM: Myopic traction maculopathy; DSM: Dome shaped macula; CNV: Choroidal neovascularization; CT: Choroidal thickness; PDCA: Peripapillary diffuse choroidal atrophy; LCs: Lacquer cracks

## Declarations

### Acknowledgements

Not applicable.

### Authors' contributions

Rong-rong Zhang designed the study, collected data, analyzed data, interpreted data, preparation of manuscript and revised the manuscript; Yan Yu and Yin-fen Hou collected data and analyzed data;

Chang-fan Wu designed the study, analyzed data, interpreted data and revised the manuscript. All authors read and approved the manuscript.

## Funding

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## Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

This study was approved by the ethical committee of Wannan Medical College Yijishan Hospital (2019A052). Permission to collect data was included under ethics approval. The informed consent was exempt according to the Institutional Review Board because each patient record was anonymized and deidentified prior to analysis.

## Consent for publication

All the participants or legal guardians of the participants in the manuscript agree to publish the images.

## Competing interests

The authors declare that they have no competing interests.

## Author details

Department of Ophthalmology, Yijishan Hospital of Wannan Medical College, Wuhu 241001, Anhui Province, China.

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## Tables

**Table 1 Inter-observer agreement for each lesion type**

Types	Weighted Fleiss $\kappa$	95% CI
A	0.651	0.602-0.700
T	0.734	0.689-0.779
N	0.702	0.649-0.755

**Table 2 Inter-observer and intra-observer agreement ( $\kappa$ ) according to the level of training**

	Inter-observer	Intra-observer
Attendings	$\kappa$ (95%CI)	$\kappa$ (95%CI)
A	0.764 (0.670-0.858)	0.824 (0.765-0.883)
T	0.836 (0.771-0.901)	0.866 (0.819-0.913)
N	0.819 (0.727-0.911)	0.892 (0.829-0.955)
Residents		
A	0.594 (0.482-0.706)	0.796 (0.698-0.894)
T	0.715 (0.599-0.831)	0.853 (0.812-0.894)
N	0.624 (0.538-0.710)	0.851 (0.796-0.906)

**Table 3 Inter-observer and intra-observer agreement for each lesion sub-type**

Sub-types	Inter-observer		Intra-observer	
	K	95%CI	K	95%CI
A1	0.563	0.465-0.661	0.885	0.834-0.936
A2	0.529	0.402-0.656	0.889	0.840-0.938
A3	0.747	0.616-0.878	0.904	0.845-0.963
A4	0.722	0.599-0.845	0.896	0.843-0.949
T0	0.729	0.609-0.849	0.960	0.931-0.989
T1	0.713	0.566-0.860	0.892	0.794-0.990
T2	0.711	0.595-0.827	0.893	0.820-0.966
T3	0.662	0.568-0.756	0.873	0.785-0.961
T4	0.762	0.615-0.909	0.890	0.812-0.968
T5	0.829	0.666-0.992	0.903	0.819-0.987
N0	0.742	0.560-0.924	0.917	0.858-0.976
N1	0.471	0.393-0.549	0.884	0.826-0.943
N2a	0.763	0.630-0.896	0.901	0.855-0.948
N2s	0.835	0.706-0.964	0.893	0.820-0.966

## Figures

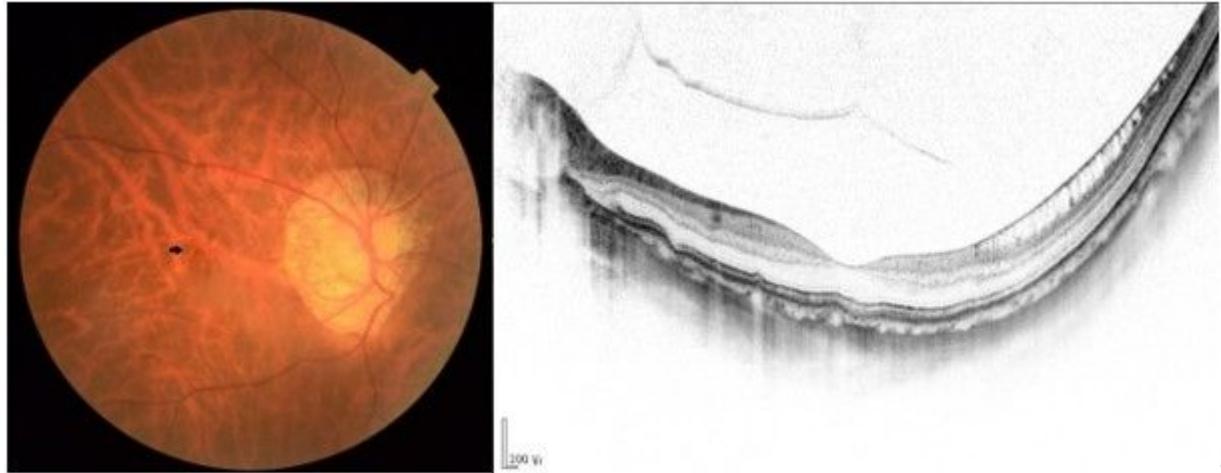
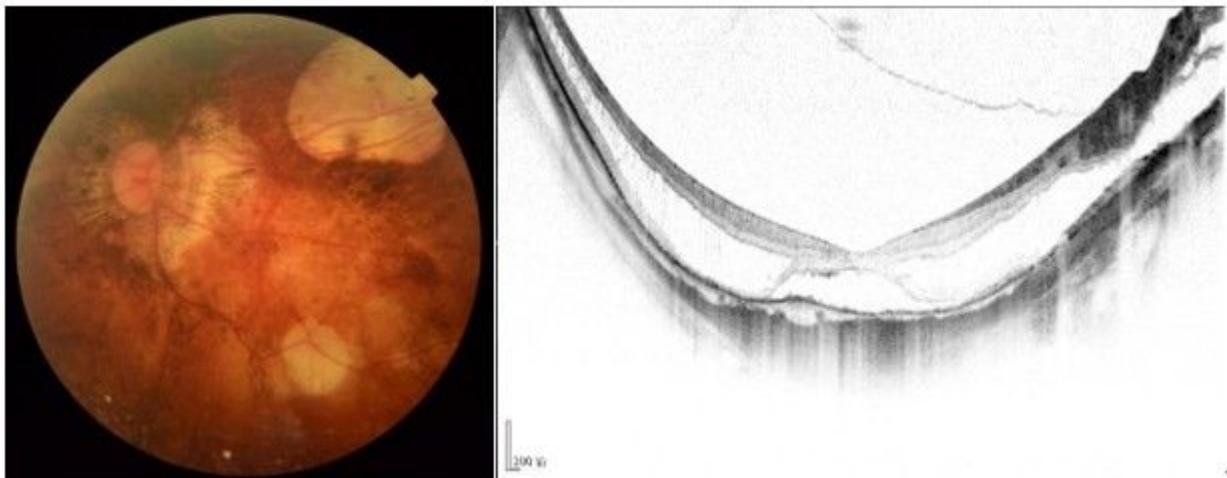


Figure 1

Highly myopic eye with tessellated fundus, outer erfoveoschisis, and macular lacquer cracks (black arrow) would be classified as stage A1T1N1 by attending ophthalmologists, while classified as stage A1T1N0 by ophthalmic residents.



**Figure 1**

Highly myopic eye with patchy atrophy, foveal detachment, and no signs of choroidal neovascularization (CNV) would be classified as stage A3T3N0 both in ophthalmologists with different qualifications.

## Supplementary Files

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