Distribution and association of visual impairment with myopic maculopathy across age groups among highly myopic eyes – based on the new classification system (ATN)

Luyao Ye,[1,2][†] Qiuying Chen,[1,2][†] Guangyi Hu,[1,2] Jiamin Xie,[1,2] Hanyi Lv,[1,2] Ya Shi,[1,2] Yao Yin,[1] Jianfeng Zhu,[1] Ying Fan,[2‡] Jiangnan He[1‡] and Xun Xu[1,2]

[1]Department of Preventative Ophthalmology, Shanghai Eye Disease Prevention and Treatment Center, Shanghai Eye Hospital, Shanghai, China
[2]Department of Ophthalmology, Shanghai General Hospital, National Clinical Research Center for Eye Diseases, Shanghai Key Laboratory of Ocular Fundus Diseases, Shanghai Engineering Center for Visual Science and Photomedicine, Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases, Shanghai Jiao Tong University, Shanghai, China

ABSTRACT.

Purpose: To investigate the percentages and risk factors for visual impairment (VI) across age groups in a highly myopic cohort with a wide range of age (18–93 years).
Methods: A total of 2099 eyes (1220 participants) were enrolled. All participants underwent detailed ocular examinations. Myopic maculopathy (MM) was assessed as myopic atrophy maculopathy (MAM), myopic traction maculopathy (MTM) or myopic neovascular maculopathy (MNM) based on the ATN system.
Results: Most participants younger than 50 years had normal vision, while the cumulative risk of VI and blindness gradually increased after 50–59 years. The percentage of each type of MM increased nonlinearly with ageing (all p < 0.001), with an accelerated period of increase after 45 years for MAM, and after 50 years for MTM and MNM. Axial length (AL) ≥30 mm was the only associated factor for mild VI or worse in participants aged 18–39 years (p < 0.001). Older age, AL ≥30 mm and the presence of MAM were predictors for mild VI or worse in the group aged 40–49 years (all p < 0.05). In participants aged ≥50 years, older age, female sex, longer AL and increased severity of MM were risk factors for VI and blindness (all p < 0.05).
Conclusion: The percentages of MM and related VI increased nonlinearly with older age, with a turning point at 45 years for MAM, preceding that of MTM, MNM and VI by 5 years, warranting future longitudinal studies to confirm. Different age groups presented different risk factors for VI. Timely screening should be in place for middle-aged high myopes.

Key words: cross-sectional study – high myopia – myopic maculopathy – visual impairment

Introduction

A worldwide 'Myopia Boom', with an increasing trend of high myopia, was noted most markedly in East and Southeast Asia (Morgan et al. 2012; Dolgin 2015; Holden et al. 2016). In some urban areas, 80–90% of teenagers completing high school develop myopia and 10–20% have high myopia (Lin et al. 2004; Sun et al. 2012). Complications specific to high myopia are the main reasons for visual acuity (VA) loss, including macular atrophy, choroidal neovascularization (CNV) and myopic traction maculopathy (MTM) (Ohno-Matsui et al. 2016c). Myopic maculopathy (MM) has become the major cause of irreversible visual impairment (VI) in both Asian (Hsu et al. 2004; Tang et al. 2015; Fricke et al. 2018) and Western countries (Buch et al. 2004; Verhoeven et al. 2015), and VI associated with MM is estimated to grow to 55.7 million people by 2050 (Fricke et al. 2018).

Several previous studies have reported the distribution of MM (Liu et al. 2010; Asakuma et al. 2012; Wong et al. 2018; Xiao et al. 2018; Fang et al. 2019; Hopf et al. 2019; Zhao et al. 2020) and VI (Shih et al. 2006; Wong et al.

2018; Jiang et al. 2020) in high myopes. However, most studies were conducted on patients aged ≥40 years. Koh et al. (2016) have explored the characteristics of MM in a Singaporean highly myopic cohort on male participants aged 19–25 years, while the distribution of VI has not been revealed. The ZOC-BHVI study has explored the rates of MM and VI in a Chinese highly myopic cohort with an age range of 7–70 years (Xiao et al. 2018; Jiang et al. 2020). However, half of the patients were under 19 years of age and patients were categorized into only two age subgroups: 19–39 and ≥40 years. Therefore, the distribution of MM and VI in relation to age was not fully clarified, especially among middle-aged patients.

Increased severity of MM has been considered as a risk factor for VI (Wong et al. 2018; Fang et al. 2019; Jiang et al. 2020; Zhao et al. 2020). MM was defined to include the following specific signs: staphyloma, lacquer cracks (LCs), Fuchs' spot and myopic chorioretinal thinning or atrophy before 2015 (Liu et al. 2010; Asakuma et al. 2012). Then, a simplified classification system, named International Photographic Classification and Grading System for myopic maculopathy (META-PM), was proposed (Ohno-Matsui et al. 2015). However, this atrophy-centred system did not take MTM into consideration, and myopic neovascular maculopathy (MNM) was classified as 'plus lesions'. Jorge Ruiz-Medrano et al. proposed the ATN classification and grading system, which integrates atrophic (A), tractional (T) and neovascular (N) alterations in the combined use of colour fundus images and optical coherence tomography (Ruiz-Medrano et al. 2019). The ATN system is a simple but comprehensive classification system with high reliability and reproducibility (Ruiz-Medrano et al. 2020; Zhang et al. 2021) and has been successfully applied in several studies to grade MM (Chen et al. 2019; Hsia et al. 2021; Li et al. 2021; Ruiz-Moreno et al. 2021). Based on this new classification system, the impact of MTM and MNM on VI could be assessed.

Therefore, a highly myopic cohort with a wide range of age was conducted to explore the distribution and association of VI and MM across age groups, especially filling the gaps in the 18–40 age group. Additionally, the ATN classification system was adopted to comprehensively and deeply investigate the epidemiological characteristics of three types of MM.

Methods

Study population

The Shanghai High Myopia Study for Adults (SHMSA) is an ongoing highly myopic cohort study, which started in 2016 at Shanghai Eye Diseases Prevention and Treatment Center in Shanghai, China. Individuals aged ≥18 years, with spherical power ≤−6.00 D or axial length (AL) ≥26 mm in either eye, were invited to register for the present study. The exclusion criteria were secondary myopia, previous intraocular or refractive surgery except for cataract surgery (having cataract surgery or not would not influence the identification of MM related VI), corneal opacity, severe cataract, glaucoma, retinal pathology nonrelated to high myopia (e.g. diabetic retinopathy, age-related macular degeneration and optic neuropathy), severe systemic diseases and poor-quality images for grading MM. AL ≥26 mm in either eye was adopted as the inclusion criteria in the present study, considering the key role of AL elongation playing in the development and progression of MM (Fang et al. 2018) and the influence of the cataract or cataract surgery history on myopic spherical equivalent (SE). The study protocol was approved by the Ethics Committee of Shanghai General People's Hospital, Shanghai, China (Approval number: 2015KY156), adhering to the tenets of the Declaration of Helsinki. Written informed consent forms were obtained from all participants.

Ophthalmic examinations

All study participants underwent a standardized clinical interview and comprehensive ophthalmic examinations, including measurement of AL using an optical low-coherence reflectometry (Lenstar LS-900; Haag-Streit AG, Koeniz, Switzerland), assessment of SE using an autorefractor (model KR-8900; Topcon, Tokyo, Japan), slit-lamp biomicroscopy and colour fundus examination with swept-source optical coherence tomography (model DRI OCT-1 Atlantis; Topcon Corp., Tokyo, Japan). Presenting distance VA in the logarithm of the minimum angle of resolution (logMAR) was assessed using the Early Treatment Diabetic Retinopathy Study chart at a distance of 4 m, and at 1 m for those failing to read the top line (20/200) under standard lighting (85 cd/m^2) with participants' habitual correction. VA was recorded as the smallest line read with one or no errors. Participants with presenting distance VA worse than 20/32 in either eye were refracted with subjective refraction to achieve best-corrected VA. According to the definition of the World Health Organization (WHO), VI was defined as VA of 20/400 to <20/63; blindness was defined as VA <20/400. Additionally, eyes with VA ≥20/63 were categorized into normal vision (VA ≥20/32) and mild VI (20/63 to <20/32; Zhao et al. 2018). Participants with counting fingers, hand motion, light perception and no light perception, who were unable to make out any numbers at 1 m, were classified into blindness but excluded during the quantified calculation for mean VA.

Cataract was classified and graded according to the Lens Opacity Classification System (LOCS) II standard colour photographs (Chylack et al. 1989). Participants were classified as 'no or early cataract' if nuclear, cortical and posterior subcapsular lens opacity was LOCS II grade NI, CI or PSCI or less. Participants were classified as 'advanced cataract' if lens opacity was NII-III, CII-III or PSCII-III respectively. Severe cataract that was LOCS II grade equal to or greater than NIV, CIV and PSCIV were excluded.

Definition and classification of MM

The new classification and grading system (ATN) for MM (Ruiz-Medrano et al. 2019) was adopted in the present study, which contained three myopic alterations. Atrophic alterations were classified into five categories: A0, no myopic retinal lesions; A1, tessellated fundus only; A2, diffuse chorioretinal atrophy (DCA); A3, patchy chorioretinal atrophy; and A4, complete macular atrophy. The eyes with a grade of A2 or higher were defined as having myopic atrophy maculopathy (MAM). The tractional alterations were classified into six categories: T0, no macular schisis; T1, inner or outer foveoschisis; T2, inner and outer foveoschisis; T3, foveal retinal detachment (FRD); T4, full-thickness macular hole (MH); and T5,

MH and FRD (MHRD). The eyes with a grade of T1 or higher were defined as having MTM. The neovascular alterations were classified into four categories: N0, no myopic CNV; N1, macular LCs; N2a, active CNV; and N2s, scar or Fuch's spot. The eyes with a grade of N1 or higher were defined as having MNM. Posterior staphyloma, a representative feature of pathologic myopia (Ohno-Matsui et al. 2016a–c), was identified separately apart from the ATN classification system according to the definition in the META-PM (Ohno-Matsui et al. 2015). The classification and grading of MM and posterior staphyloma were performed by two independent, well-trained graders (LY and QC), who were masked to the demographic, refraction and ocular biometry information. The weighted kappa (95% confidence interval) for inter-grader agreement was 0.972 (0.963–0.980) for atrophic alterations, 0.985 (0.972–0.997) for tractional alterations, 0.975 (0.964–0.986) for neovascular alterations and 0.951 (0.937–0.964) for posterior staphyloma, indicating a good agreement. 91 of 2099 (4.3%) eyes were adjudicated by a retinal specialist (YF). The contrast, brightness, background pigmentation and photograph quality were taken into account during the assessment.

Statistical analysis

Both eyes were included in this study in accordance with the inclusion/exclusion criteria. Generalized estimating equation regression models were used to evaluate the association between the ocular parameters to account for the correlation between the two eyes. The baseline characteristics were summarized using counts (percentages) for categorical data and mean ± standard deviation for continuous data. Intergroup differences were tested with the Student's t-test or analysis of variance for continuous data, and with chi-squared or Fisher's exact test for categorical data. The p value for trend was tested using multivariable logistic regression analysis adjusting for sex to reveal the association between age and AL, adjusting for sex and AL to explore the relationship of age with VA loss, MAM, MTM, MNM and posterior staphyloma. The Joinpoint regression analysis fits a model that identifies time points (joinpoints) in

which trends change significantly (Cayuela et al. 2004; Statistical Methodology & Applications Branch 2020). This analysis is used to assess the trends in the percentages of MAM, MTM, MNM and posterior staphyloma with age, with a maximum number of joinpoint set to one on a linear scale. The cumulative risk of VI and blindness was estimated by MM categories using the Kaplan–Meier product limit analysis (Tideman et al. 2016). Multivariable logistic regression analysis was performed for age, sex, AL and MAM as independent variables to predict mild VI or worse in groups aged 18–39 and 40–49 years. Considering the separate data in grades of A4, T3–T5 and N2a, penalized maximum likelihood estimation was conducted for age, sex, AL, MAM, MTM, MNM, cataract and phakic eyes as independent variables to predict VI and blindness for participants aged ≥50 years. Fundus lesion severity is significantly related to posterior staphyloma; thus, only fundus lesion level was included in the multiple regression analysis models. A p value of less than 0.05 was considered statistically significant. Statistical Analysis System (v. 9.3; SAS Institute, Cary, NC, USA) and Joinpoint Regression Program (v. 4.8.0.1; National Cancer Institute) were used for statistical analyses.

Results

Baseline characteristics

Among 2259 eyes of 1332 participants who were initially screened, 160 eyes were excluded for the following reasons: two eyes had secondary myopia, 26 had a history of surgery other than cataract, eight had corneal opacity, 73 had severe cataract, nine had glaucoma, 30 had retinal pathology not related to high myopia, and 12 had poor-quality images for grading MM. In the end, a total of 2099 eyes of 1220 participants with high myopia were included in this study. No significant differences in ocular biometry were found between the two eyes using the generalized estimating equation regression models.

Table 1 summarizes the demographic and clinical characteristics of the participants. The mean age was 47.74 ± 20.08 years (range, 18–93 years), the mean AL was 27.60 ± 1.52 mm (range, 26.00–33.68 mm), the mean SE (after

excluding pseudophakic eyes) was −8.74 ± 4.47 D (range, −4.00 D to −25.50 D), and the mean VA (logMAR [Snellen]) was 0.19 ± 0.28 (~20/31). Among 2099 highly myopic eyes, there were 319 (15.2%), 199 (9.5%) and 63 (3.0%) eyes having mild VI, VI and blindness respectively; 1395 (66.5%) eyes having normal fundus or tessellated fundus only, and 704 (33.5%) eyes having MM, including 642 (30.6%) eyes with MAM, 271 (12.9%) eyes with MTM and 460 (21.9%) eyes with MNM. Participants with either type of MM were significantly older; had longer AL; had higher percentages of mild VI, VI, blindness, female sex and posterior staphyloma compared with those without MM (all p < 0.001).

Distribution of VI and MM across age groups

The percentages of mild VI, VI and blindness trended upward with age in adjustment for sex and AL (all p < 0.001; Table 2). Among participants younger than 50 years old, most eyes had normal vision, while few eyes presented mild VI. VI was seen only in 1 patient aged 22 years old with active CNV (N2a), and no blindness was seen. On the contrary, the percentages of mild VI, VI and blindness significantly soared up in the group aged 50–59 years, continually increasing thereafter. Further, the cumulative risk of VI and blindness was examined in relation to myopic alterations (Fig. 1). The cumulative risk of VI and blindness for each type of myopic alteration gradually increased for participants aged 50–59 years, whereas eyes with N2a were increasingly visually impaired for participants aged 20 years and older.

Also, participants with older age tended to have higher percentages of MAM, MTM, MNM and posterior staphyloma after adjusting for sex and AL (all p for trend < 0.001, Table 2). MM and posterior staphyloma were uncommon in participants younger than 50 years (41 of 1033 and 49 of 1033 respectively), including 37 eyes with DCA (A2), 2 eyes with inner foveoschisis (T1), 1 eye with active CNV (N2a) and 1 eye with patchy atrophy coexisted with inner foveoschisis and LCs (A3T1N1). On the contrary, the percentages of MAM, MTM, MNM and posterior staphyloma substantially increased among participants

Table 1. Baseline characteristics and comparisons between highly myopic eyes with and without myopic maculopathy

	Total Cohort	High Myopia without MM	High Myopia with MM	p value*	MAM	MTM	MNM
No. eyes, n (%)	2099	1395 (66.5)	704 (33.5)		642 (30.6)	271 (12.9)	460 (21.9)
Age (years)	47.74 ± 20.08	38.72 ± 17.52	65.63 ± 10.63	<0.001	65.74 ± 10.79*	67.45 ± 7.57*	67.50 ± 7.28*
Female, n (%)	1006 (47.9)	652 (46.7)	441 (62.6)	<0.001	412 (64.2)*	187 (69.0)*	300 (65.2)*
AL (mm)	27.60 ± 1.52	26.94 ± 0.80	28.94 ± 1.74	<0.001	29.02 ± 1.75*	29.55 ± 1.62*	29.59 ± 1.61*
PS, n (%)	845 (40.3)	190 (13.6)	655 (93.0)	<0.001	601 (93.6)*	264 (97.4)*	456 (99.1)*
VA, LogMAR[†]	0.19 ± 0.28	0.07 ± 0.12	0.43 ± 0.35	<0.001	0.44 ± 0.36*	0.54 ± 0.38*	0.52 ± 0.37*
(Snellen)	~20/31	~20/23	~20/54		~20/55	~20/69	~20/66
20/63 to <20/32	319 (15.2)	101 (7.2)	218 (31.0)	<0.001	196 (30.5)*	75 (27.7)*	143 (31.1)*
20/400 to <20/63	200 (9.5)	10 (0.7)	189 (26.8)	<0.001	177 (27.6)*	93 (34.3)*	156 (33.9)*
<20/400	63 (3.0)	0	63 (8.9)	<0.001	59 (9.2)*	42 (15.5)*	59 (12.8)*

AL = axial length, LogMAR = logarithm of minimal angle of resolution, MAM = myopic atrophy maculopathy, MM = myopic maculopathy, MTM = myopic traction maculopathy, MNM = myopic neovascular maculopathy, PS = posterior staphyloma, VA = visual acuity.
The continuous variables were described as mean ± standard deviation, and the categorical variables were listed as number (percentage).
* p < 0.001 for comparisons between high myopia without MM and MAM, MTM or MNM using Student's t-test for continuous data, and using chi-squared or Fisher's exact test for categorical data.
[†] p Value for comparisons between high myopia with and without MM using Student's t-test for continuous data, and using chi-squared or Fisher's exact test for categorical data.
[§] 47 eyes with counting fingers, hand motion, light perception or no light perception were excluded from the mean VA calculation.

Table 2. Distribution of myopic maculopathy and visual impairment by age groups

	18–29	30–39	40–49	50–59	60–69	≥70	p for trend
No. eyes, n (%)	616 (29.3)	231 (11.0)	186 (8.9)	201 (9.6)	598 (28.5)	267 (12.7)	
Female, n (%)	261 (42.4)	131 (56.7)	92 (49.5)	116 (57.7)	348 (58.2)	145 (54.3)	<0.001
AL, mm	27.01 ± 0.81	26.91 ± 0.91	27.01 ± 0.96	28.01 ± 1.76	28.21 ± 1.80	28.34 ± 1.69	<0.001*
VA, LogMAR[†]	0.03 ± 0.08	0.03 ± 0.08	0.06 ± 0.10	0.25 ± 0.29	0.32 ± 0.29	0.47 ± 0.37	<0.001[§]
(Snellen)	~20/21	~20/21	~20/23	~20/36	~20/42	~20/59	
20/63 to <20/32	11 (1.8)	5 (2.2)	12 (6.5)	31 (15.4)	175 (29.3)	85 (31.8)	<0.001[§]
20/400 to <20/63	1 (0.2)	0	0	34 (16.9)	95 (15.9)	70 (26.2)	<0.001[§]
<20/400	0	0	0	4 (2.0)	29 (4.8)	30 (11.2)	<0.001[§]
MAM, n (%)	14 (2.3)	8 (3.5)	16 (8.6)	74 (36.8)	329 (55.0)	201 (75.3)	<0.001[§]
MTM, n (%)	0	2 (0.9)	1 (0.5)	33 (16.4)	138 (23.1)	97 (36.3)	<0.001[§]
MNM, n (%)	1 (0.2)	1 (0.4)	0	48 (23.9)	257 (43.0)	153 (57.3)	<0.001[§]
PS, n (%)	23 (3.7)	7 (3.0)	19 (10.2)	101 (50.2)	457 (76.4)	238 (89.1)	<0.001[§]

AL = axial length, LogMAR = logarithm of minimal angle of resolution, MAM = myopic atrophy maculopathy, MTM = myopic traction maculopathy, MNM = myopic neovascular maculopathy, PS = posterior staphyloma, VA = visual acuity.
The continuous variables were described as mean ± standard deviation and the categorical variables were listed as counts (percentages).
*p for trend for comparisons across age groups using multivariable regression analysis adjusting for sex.
[†] p for trend for comparisons across age groups using multivariable regression analysis adjusting for sex and AL
[§] 47 eyes with counting fingers, hand motion, light perception or no light perception were excluded from the mean VA calculation.

aged 50 years or older, accompanied by increased severe alterations including macular atrophy (A4), MH (T3), FRD (T4), MHRD (T5) and scar/Fuch's spot (N2s) (Fig. 2). Furthermore, a one joinpoint model was established to test for any identified statistically significant trend changes (Fig. 3). The percentages of MAM and posterior staphyloma did not significantly change with age for participants younger than 45 years, while an ever-increasing trend was detected for participants aged ≥45 years (both p < 0.001). Similar patterns were observed in terms of MTM and MNM, although with a different joinpoint of 50 years (both p < 0.001).

Distribution of VI stratified by sex, AL and MM in the total cohort and in different age groups

In the total cohort, the percentages of mild VI, VI and blindness were higher in female participants (all p < 0.001); in eyes with longer AL (all p < 0.001); in eyes with the presence of more severe MAM (all p < 0.001), MTM (all p < 0.001) or MNM (all p < 0.001); and in eyes with the presence of posterior staphyloma (all p < 0.001). Notably, few or no mild VI was seen in eyes with the presence of advanced alterations, including grades of T3–T5, N2a and N2s, most or all of which presented VI and blindness instead (Table 3).

Based on the previous findings that the cumulative risk of VI and blindness gradually increased after 50–59 years, the risk factors for VI were further explored in different age subgroups (<50 years and ≥50 years; Table 3). Similar associations of VI with age, AL and MM were found in the age group ≥50 years as found in the total cohort. Among participants younger than 50 years, mild VI or worse (VA <20/32) was adopted for classification driven by the almost absence of VI and blindness. Eyes with longer AL (p < 0.001), and eyes with the presence of MAM (p = 0.03) or posterior staphyloma (p < 0.001) presented a higher percentage of mild VI or worse;
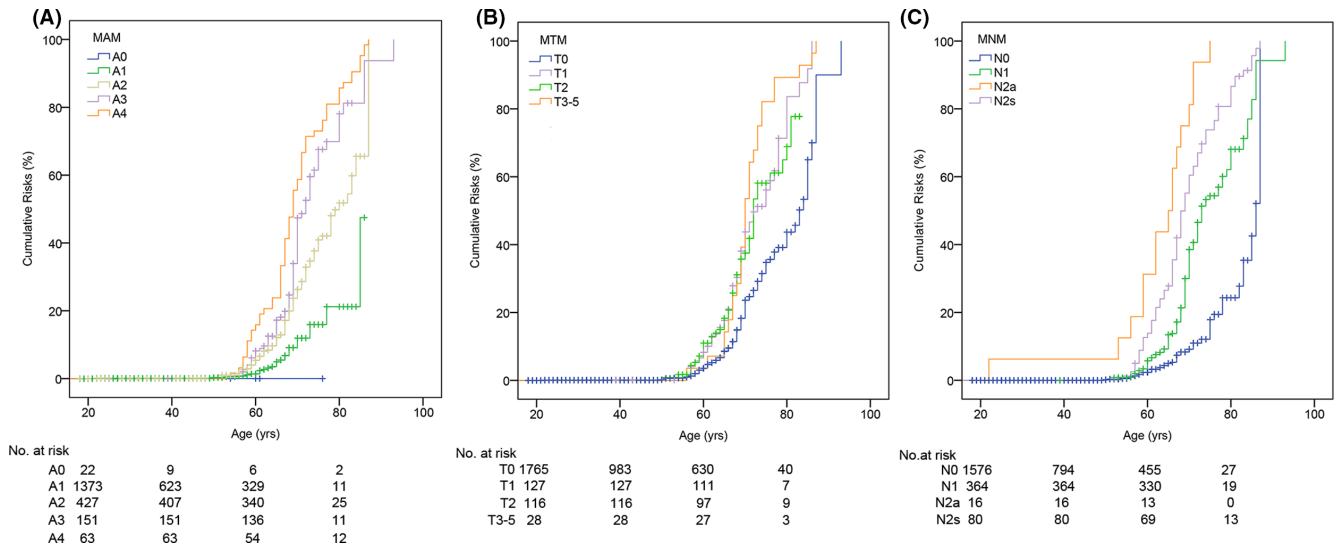
Fig. 1. The cumulative risk of visual impairment and blindness for different types of myopic maculopathy. The number of persons at risk at each decade per myopic alteration category was presented below. (A) The cumulative risk of visual impairment and blindness for myopic atrophy maculopathy (MAM). For participants aged 80 years, the cumulative risk (standard error) of VI and blindness was 0.0% (0.00) for A0, 21.2% (0.06) for A1, 51.8% (0.05) for A2, 78.1% (0.06) for A3 and 85.7% (0.04) for A4. (B) The cumulative risk of visual impairment and blindness for myopic tractional maculopathy (MTM). For participants aged 80 years, the cumulative risk (standard error) of VI and blindness was 43.7% (0.04) for T0, 83.6% (0.07) for T1, 68.9% (0.07) for T2 and 89.3% (0.06) for T3–T5. (C) The cumulative risk of visual impairment and blindness for myopic neovascular maculopathy (MNM). For participants aged 80, the cumulative risk (standard error) of VI and blindness was 24.3% (0.05) for N0, 68.1% (0.05) for N1, 100.0% (0.00) for N2a and 86.6% (0.04) for N2s.

however, the percentage did not significantly differ when stratified by sex, presence of MTM or MNM (p = 0.06–1.00).

To investigate whether risk factors for mild VI would differ between young adults and middle-aged adults among participants younger than 50 years, the associations of mild VI with candidate factors were further analysed in subgroups stratified by the age of 40 based on clinical experience (Table 4). Among participants younger than 40 years, eyes with longer AL (p < 0.001) and eyes with the presence of MNM (p = 0.04) or posterior staphyloma (p = 0.02) presented a higher percentage of mild VI and worse. The percentage of mild VI and worse was higher in eyes with longer AL (p = 0.02) and eyes with the presence of MAM (p = 0.01) or posterior staphyloma (p < 0.001) in participants aged 40–49 years. No significant difference was observed when stratified by sex or presence of MTM in either subgroup (p = 0.25–1.00).

Associations of VI with age, AL and MM in different age groups

Among participants younger than 40 years, AL longer than 30 mm (odds ratio [OR] = 170.269; p < 0.001) was a risk factor for mild VI or worse adjusting for age, sex and presence of MAM (p = 0.17–0.80). In the group aged 40–49 years, participants with older age (OR = 1.639, p = 0.02), AL longer than 30 mm (OR = 166.563, p = 0.003) and presence of MAM (OR = 6.465, p = 0.03) were more likely to develop mild VI or worse adjusting for sex. For participants aged 50 years or old, older age (OR = 1.037, p = 0.02), female sex (OR = 1.875, p = 0.003), longer AL (28–30 mm, OR = 2.159, p = 0.004; ≥30 mm, OR = 3.541, p < 0.001), presence of MAM (A2, OR = 2.342, p = 0.004; A3, OR = 3.671, p < 0.001; A4, OR = 164.547, p = 0.001), presence of MTM with grades of T3–T5 (OR = 164.202, p = 0.001), presence of MNM with grades of N2a (OR = 280.733, p < 0.001) or N2s (OR = 7.921, p < 0.001), advanced cataract (OR = 2.654, p = 0.01) and phakic eyes (OR = 2.874; p < 0.001) were predictors for VI and blindness (Fig. 4).

Discussion

The present study was novel in investigating the distribution and association of VI and three types of MM across different age groups in a large Chinese highly myopic cohort with a wide range of age (18–93 years) using the ATN classification system, especially filling the gaps in the 18–40 age group and in the field of MTM features. The results suggested that the percentages of MM and VI increased nonlinearly with older age, with a turning point at 45 years for MAM, 50 years for MTM, MNM and VI. Also, this study identified that different age groups presented different risk factors for VI and emphasized that high attention, timely screening and close monitoring were needed for middle-aged high myopes. Priority should also be given to extreme long AL in young participants (<40 years), female sex and increased severity of MM in older participants (≥50 years), to reduce future vision loss and blindness. However, the clinical relevance of these results cannot be determined from this cross-sectional study and warrant future longitudinal study.

Mild VI, VI and blindness were seen in 15.2%, 9.5% and 3.0% of participants in the present study respectively. The percentage data had a good agreement with the rates of VI and blindness in a highly myopic cohort from Taiwan (28.6%) (Shih et al. 2006) using the US definition, but were higher than those in the ZOC-BHVI study using the WHO definition (4.1%), probably because that half of the participants were under 19 years of age (Jiang et al.
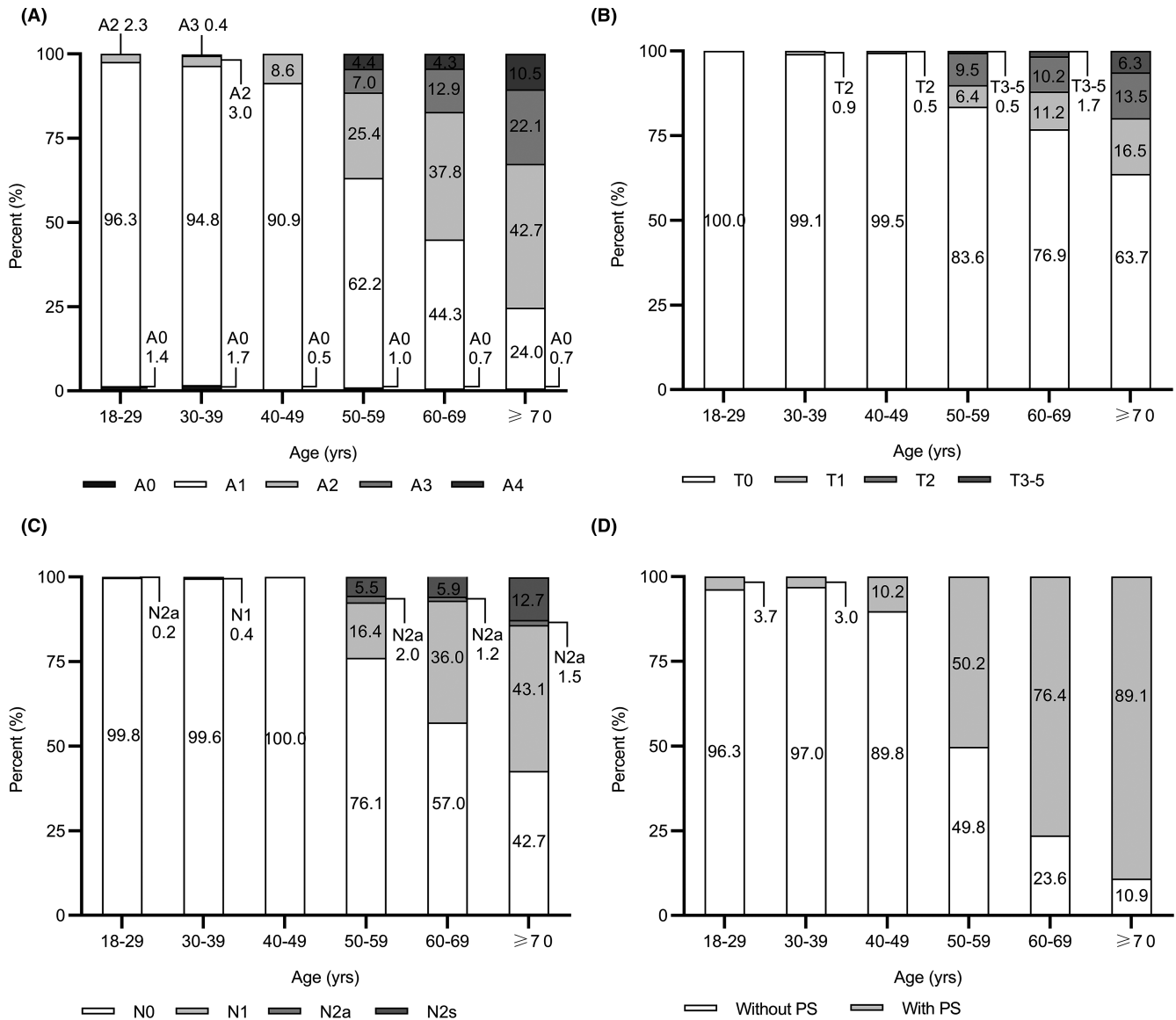
Fig. 2. Distributions of different categories of myopic maculopathy and posterior staphyloma by age groups. (A) Myopic atrophy maculopathy, (B) myopic traction maculopathy, (C) myopic neovascular maculopathy and (D) posterior staphyloma.

2020). MAM or MNM was seen in 682 of 2099 eyes (32.5%) in this highly myopic cohort, which was lower than the percentage of MM in two hospital-based highly myopic cohorts from China (54.5%) (Zhao et al. 2020) and Japan (80.4%) (Fang et al. 2019) based on the META-PM, but was in line with the prevalence of MM in a population-based study of high myopes from Singapore (28.7%) (Wong et al. 2018). This suggested that the severity of the cases should be representative of high myopia in a general population setting among Eastern regions. The distribution of MTM has barely been reported and was seen in 12.9% of participants in the present study, which was lower than that in two hospital-based highly

myopic cohorts from China (41.7%) (Li et al. 2021) and Japan (23.0%) (Fang et al. 2019).

Emerging evidence suggests that older age is a risk factor for VI and MM in high myopes (Wong et al. 2018; Xiao et al. 2018; Fang et al. 2019; Hopf et al. 2019; Jiang et al. 2020; Zhao et al. 2020). However, most previous studies were conducted on participants aged ≥40 years; the development and progression pattern of VI and MM, especially among young and middle-aged high myopes, therefore, remained unrevealed. This study revealed that the cumulative risk of VI and blindness gradually increased for highly myopic participants aged 50–59 years for each type of MM, which was consistent with

the findings by Shih et al., that among high myopes with an initial best-corrected VA of ≥20/40, 97.2% of those aged 40–49 years maintained a good VA after 10 years of follow-up, whereas 19.3% of those aged 50–59 years ended up with a progression to VI (Shih et al. 2006).

In accordance with the distribution features of VI, the percentages of three types of MM and posterior staphyloma generally increased with age, despite at different turning points. MAM and posterior staphyloma had an accelerated period of increase after 45 years, preceding that of MTM or MNM by 5 years. Of note, the alteration of MAM between 45 and 49 years was limited to DCA, while more severe
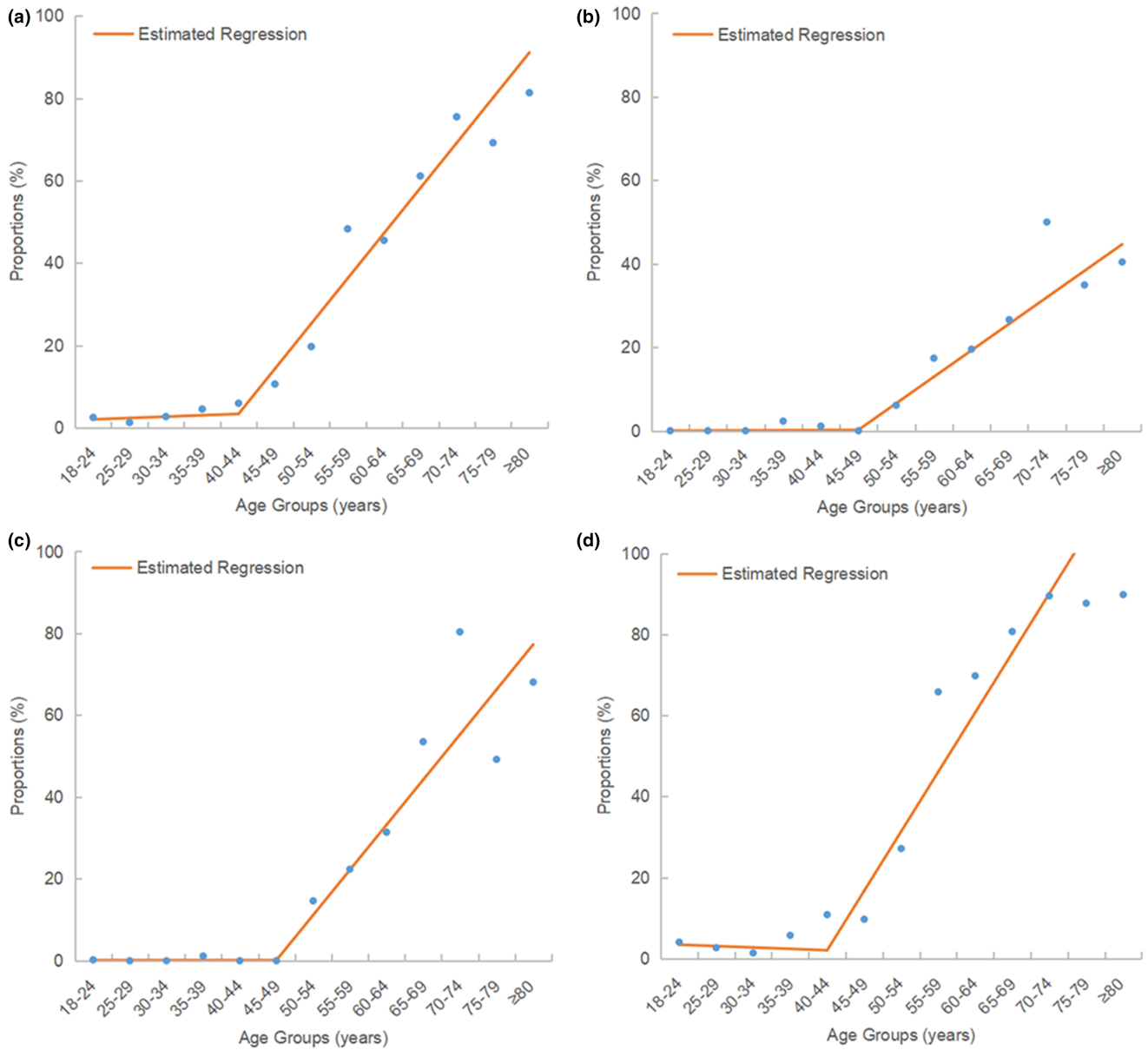
Fig. 3. Joinpoint regression analysis of myopic maculopathy percentages with age. (A) For myopic atrophy maculopathy, the estimated regression function for age <45 years: $y = 0.33x + 1.77$ (p = 0.64); for age ≥45 years: $y = 10.96x - 51.38$ (p < 0.001). (B) For myopic traction maculopathy, the estimated regression function for age <50 years: $y = 0.33x + 1.77$ (p = 0.64); for age ≥50 years: $y = 10.96x - 51.38$ (p < 0.001). (C) For myopic neovascular maculopathy, the estimated regression function for age <50 years: $y = 0.33x + 1.77$ (p = 0.64); for age ≥50 years: $y = 10.96x - 51.38$ (p < 0.001). (D) For posterior staphyloma, the estimated regression function for age <45 years: $y = -0.34x + 3.77$ (p = 0.77); for age ≥45 years: $y = 14.67x - 71.30$ (p < 0.001).

alterations (patchy atrophy or macular atrophy) occurred after 50 years. Speculatively, the distribution features of MM suggested the possible pathologic mechanisms during the progression of MM that progressive choroidal thinning might firstly play a role in the progression from no maculopathy to tessellation and to DCA (Fang et al. 2019), while other mechanisms such as Bruch membrane defect (Ohno-Matsui et al. 2016a–c; Fang et al. 2019), choroidal ischaemia (Chen et al. 2019) or mechanical stretching (Chen et al. 2019),

involved in the pathogenesis of patchy atrophy, macular atrophy, MNM and MTM, occurred several years later. Local deformity of eyes might also be one of the first features to occur in pathologic myopia. Previous studies have found that posterior staphyloma was more frequent in the eyes with DCA, MTM or lacquer cracks than those without (Steidl & Pruett 1997; Forte et al. 2008). But the underlying relationship of posterior staphyloma with other alterations (causal or concomitant) remained unclear.

Altogether, MM could be an age-related disease that retinal damage required quite a long time to develop, with an accelerated worsening period in participants over 50 years of age, which requires future longitudinal studies to confirm. Interestingly, this trend was also seen in age-related diseases such as cardiovascular diseases (Virani et al. 2020) and type 2 diabetes mellitus (Visaria et al. 2019), which were uncommon in young adults; however, the prevalence was much higher in the age group of 40–60 years. These

Table 3. Distribution of visual impairment stratified by sex, axial length, myopic maculopathy in total cohort and in different age groups

| | Total Cohort (n = 2099) | | | Age Groups (years) | | | |
| | | | | <50 (n = 1033) | ≥50 (n = 1066) | | |
	Mild VI	VI	Blindness	Mild VI and worse	Mild VI	VI	Blindness
Sex							
Male (n = 1006)	117 (11.6)	66 (6.6)	12 (1.2)	11 (2.0)	107 (23.4)	65 (14.2)	12 (2.6)
Female (n = 1093)	203 (18.6)	133 (12.2)	51 (4.7)	18 (3.7)	185 (30.4)	133 (21.8)	51 (8.4)
p Value	<0.001	<0.001	<0.001	0.10	0.01	0.002	<0.001
AL (mm)							
26–<28 (n = 1465)	154 (10.5)	39 (2.7)	13 (0.9)	18 (2.0)	136 (24.1)	39 (6.9)	13 (2.3)
28–<30 (n = 409)	98 (24.0)	75 (18.3)	22 (5.4)	6 (5.1)	92 (31.6)	75 (25.8)	22 (7.6)
≥30 (n = 203)	60 (29.6)	82 (40.4)	26 (12.8)	4 (57.1)	57 (29.1)	81 (41.3)	26 (13.3)
p Value	<0.001	<0.001	<0.001	<0.001	0.04	<0.001	<0.001
Atrophic alteration							
A0&A1 (n = 1457)	124 (8.5)	22 (1.5)	4 (0.3)	23 (2.3)	102 (22.1)	21 (4.5)	4 (0.9)
A2 (n = 428)	151 (35.3)	86 (20.1)	13 (3.0)	6 (16.2)	145 (37.1)	86 (22.0)	13 (3.3)
A3 (n = 151)	45 (29.8)	58 (38.4)	16 (10.6)	0	45 (30.0)	58 (38.7)	16 (10.7)
A4 (n = 63)	0	33 (52.4)	30 (47.6)	..	0	33 (52.4)	30 (47.6)
p Value	<0.001	<0.001	<0.001	0.03	<0.001	<0.001	<0.001
Tractional alteration							
T0 (n = 1828)	245 (13.4)	106 (5.8)	21 (1.1)	29 (2.8)	217 (27.2)	105 (13.2)	21 (2.6)
T1 (n = 127)	35 (27.6)	49 (38.6)	11 (8.7)	0	35 (28.2)	49 (39.5)	11 (8.9)
T2 (n = 116)	40 (34.5)	31 (26.7)	16 (13.8)	..	40 (34.5)	31 (26.7)	16 (13.8)
T3–T5 (n = 28)	0	13 (46.4)	15 (53.6)	..	0	13 (46.4)	15 (53.6)
p Value	<0.001	<0.001	<0.001	1.00	<0.001	<0.001	<0.001
Neovascular alteration							
N0 (n = 1639)	177 (10.8)	43 (2.6)	4 (0.2)	28 (2.7)	149 (24.5)	43 (7.1)	4 (0.7)
N1 (n = 364)	136 (37.4)	106 (29.1)	20 (5.5)	0	136 (37.5)	106 (29.2)	20 (5.5)
N2a (n = 16)	0	11 (68.8)	5 (31.3)	1 (100.0)	0	10 (66.7)	5 (33.3)
N2s (n = 80)	7 (8.8)	39 (48.8)	34 (42.5)	..	7 (8.8)	39 (48.8)	34 (42.5)
p Value	<0.001	<0.001	<0.001	0.06	<0.001	<0.001	<0.001
PS							
Without PS (n = 1254)	59 (4.7)	2 (0.2)	1 (0.1)	20 (2.0)	39 (14.4)	2 (0.7)	1 (0.4)
With PS (n = 845)	260 (30.8)	198 (23.4)	62 (7.1)	9 (18.4)	252 (31.8)	196 (24.6)	62 (7.8)
p Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

AL = axial length, PS = posterior staphyloma, VA = visual acuity, VI = visual impairment.
Data were listed as counts (percentages). Mild VI was defined as VA of 20/63 to <20/32; VI was defined as VA of 20/400 to <20/63; blindness was defined as VA <20/400.
p Value for comparisons using chi-squared or Fisher's exact test.

findings would assist in suggesting the onset features and progression trends of MM and VI, guiding screening strategies for MM and providing a solid basis for clinical decision-making in terms of early detection, prognosis prediction, and follow-up planning of MM, and ultimately, preventing permanent vision loss.

Our results showed that different age groups presented different risk factors for VI. The risk of mild VI in young high myopes with extreme long AL (AL ≥30 mm) was 170.3 times higher than those with AL <28 mm and thus worth highly clinical attention. As for participants aged 40–49 years, older age and presence of MAM were risk factors for mild VI, implying that middle-aged high myopes might experience a decline in VA with ageing and the development of MAM, and were at high risk of progressing to VI within several years. Working-age adults are major contributors to social development, and VI might cause a significant socioeconomic burden, emphasizing the need for wide-covered ophthalmic screening, timely referral and close follow-ups for middle-aged high myopes.

As for high myopes aged ≥50 years, the risk of VI was 1.9 times higher in females than in males in this study, which was consistent with other studies (Zhao et al. 2018; Jiang et al. 2020). The influence of climacteric sex hormone fluctuation on ocular structures might be the potential mechanism (Lyu et al. 2015). Moreover, as indicated in previous studies (Wong et al. 2018; Fang et al. 2019; Jiang et al. 2020; Zhao et al. 2020), VI was nonlinearly associated with the severity of MAM in the age group ≥50 years that VA was significantly affected once the alterations involved macula. Regarding MTM, we found that MH, FRD and MHRD were strongly associated with VI, while neither type of foveoschisis was a risk factor for VI. Li et al. classified 1334 highly myopic eyes based on the ATN system and found that the best-corrected VA of eyes with outer foveoschisis and eyes with both inner and outer foveoschisis did not differ significantly from each other, but both were worse than that of eyes with inner foveoschisis (Li et al. 2021). A recent study by Parolini et al. raised a new MTM staging system based on two evolution patterns, foveal and retinal ones, at the OCT scans. Foveoschisis was replaced by macular schisis (MS) because schisis affected the whole retina and not only the fovea in

Table 4. Distribution of mild visual impairment and worse stratified by sex, axial length, myopic maculopathy in different age groups among patients aged <50 years

	Age Groups (years)	
	18–39 (n = 847)	40–49 (n = 186)
Sex		
Male (n = 549)	7 (1.5)	4 (4.3)
Female (n = 484)	10 (2.6)	8 (8.7)
p Value	0.33	0.25
AL (mm)		
26–<28 (n = 900)	11 (1.5)	7 (4.4)
28–<30 (n = 118)	3 (3.1)	3 (13.6)
≥30 (n = 7)	3 (60.0)	1 (50.0)
p Value	<0.001	0.02
Atrophic alteration		
A0&A1 (n = 995)	15 (1.8)	8 (4.7)
MAM (n = 38)	2 (9.1)	4 (25.0)
p Value	0.07	0.01
Tractional alteration		
T0 (n = 1030)	17 (2.0)	12 (6.5)
MTM (n = 3)	0	0
p Value	1.00	1.00
Neovascular alteration		
N0 (n = 1031)	16 (1.9)	12 (6.5)
MNM (n = 2)	1 (50.0)	–
p Value	0.04	–
PS		
Without PS (n = 984)	14 (1.7)	6 (3.6)
With PS (n = 49)	3 (10.0)	6 (31.6)
p Value	0.02	<0.001

AL = axial length, MAM = myopic atrophy maculopathy, MTM = myopic traction maculopathy, MNM = myopic neovascular maculopathy, PS = posterior staphyloma.
Data were listed as counts (percentages). Mild visual impairment and worse was defined as visual acuity of <20/32.
p Value for comparisons using chi-squared or Fisher's exact test.

most cases. The study did not find any significant difference between eyes with inner MS or inner and outer MS and eyes with predominantly outer MS (Parolini et al. 2020). These findings suggested that the impact of retinal schisis on VA is controversial and affected by the classification system. As suggested in our findings, neovascular alterations secondary to pathologic myopia, including active CNV and scar/Fuch's spot, are severe sight-threatening complications (Ohno-Matsui et al. 2016a–c). However, LCs were not risk factors for VI in the present study. This phenomenon might because the impact on VA was affected by the location and number of LCs, which has not been studied in-depth in this study. LCs, classified into MNM though, have different pathologic mechanism from the other two alterations, that is linear defects in Bruch's membrane (Ruiz-Medrano et al. 2019). Based on an 18-year follow-up of high myopes from Japan, it was deduced that 57.6% of eyes with LCs progressed to patchy atrophy with a widened Bruch's membrane defect (Fang et al. 2018). Therefore, a comprehensive classification of Bruch's membrane defects, aligned to the evolution pattern, would help to explore their association with VI for clinical management. These findings altogether suggested that more attention should be paid to the characteristics of
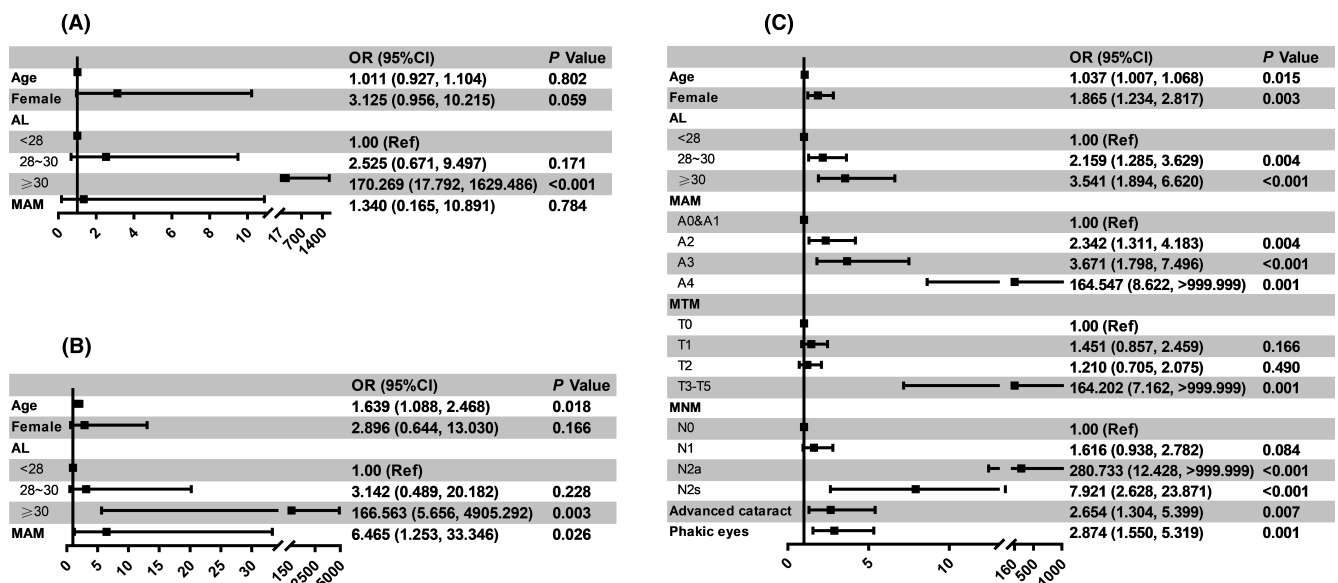

Fig. 4. Risk factors for visual impairment in different age groups. Risk factors for mild visual impairment or worse in the groups aged (A) 18–39 and (B) 40–49 years using multivariable regression analysis. (C) Risk factors for visual impairment and blindness in the group aged ≥50 years using penalized maximum likelihood estimation. AL, axial length; MAM, myopic atrophy maculopathy; MTM, myopic tractional maculopathy; MNM, myopic neovascular maculopathy.

female sex and increased severity of three types of MM among high myopes aged ≥50 years.

There are several limitations that have to be addressed. First, the possibility of a referral bias might have existed since the recruitment in this study was not population-based, and it remains unclear whether the results of this study could be applied directly to a highly myopic group in the general population. Second, owing to the cross-sectional nature of this study, the longitudinal progression and causal effects could not be determined. Third, the number of middle-aged participants (40–49 years) was relatively small. Ongoing sample size expansion and further longitudinal data would help validate the outcomes with greater reliability. Fourth, participants with severe cataract were excluded from the analysis considering its non-negligible impact on VA and quality of images. However, the characteristics of those who did not receive cataract surgery due to MM were inevitably missed in this study. Fifth, the percentage of MNM might have been underestimated since fluorescein angiography and indocyanine green angiography, the gold standard for the diagnosis of LCs and CNV, were not performed. Sixth, staphylomas located outside the posterior pole might have been missed with the absence of a wide-field imaging system, and therefore, the percentage of posterior staphyloma might have been underestimated.

In conclusion, this study revealed the distribution pattern of MM and VI with age in a highly myopic cohort as follows: MM and related VI were uncommon in young high myopes and had an accelerated worsening period at about 45 years for MAM, 50 years for MTM, MNM and VI. Although the clinical relevance of this study cannot be determined and warrant future longitudinal study, these results might help in suggesting the onset features and progression trends of MM, and guiding screening strategies and clinical decision-making for high myopia. Additionally, we emphasized that high attention, timely screening and close monitoring should be in place for middle-aged high myopes (40–49 years). Priority should also be given to extreme long AL in young participants (<40 years); to female sex and increased severity of MM in older participants (≥50 years) to reduce future vision loss and blindness.

Data availability

The data analysed during the current study are available from the corresponding author on reasonable request.

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Correspondence:
Ying Fan, MD
Department of Ophthalmology
Shanghai General Hospital
National Clinical Research Center for Eye Diseases
Shanghai Key Laboratory of Ocular Fundus Diseases
Shanghai Engineering Center for Visual Science and Photomedicine
Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases
Shanghai Jiao Tong University
No.100 Haining Road
Shanghai
200080
China
Tel: 86-13386259755
Fax: 86-21-33011075
Email: fanying0129@163.com
Jiangnan He, MPH
Department of Preventative Ophthalmology
Shanghai Eye Disease Prevention and Treatment Center
Shanghai Eye Hospital
No. 380 Kangding Road
Shanghai
200040
China
Tel: 86-18101853556
Fax: 86-21-33011075
Email: hejiangnan85@126.com

†These authors contributed equally as co-first authors.

‡These authors contributed equally as co-corresponding authors