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Original Research Article

AN UPDATED SIMPLIFIED SEVERITY SCALE FOR AGE-RELATED MACULAR DEGENERATION INCORPORATING RETICULAR PSEUDODRUSEN

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Abstract: *Age-related macular degeneration (AMD) is a progressive retinal disease that primarily affects older adults and is one of the leading causes of vision loss worldwide. Objective: This study aims to develop and validate an updated AMD severity scale that includes RPDs, evaluating its ability to predict disease progression.* ***Methods:*** *This cross-sectional study was conducted at Wah Medical College, Wah Catt A total of 155 patients were included in the study. Data from retinal imaging, visual acuity, and OCT measurements were collected and analyzed to classify patients according to the proposed AMD severity scale. Two independent retina specialists, who were blinded to the clinical outcomes, performed the grading of all imaging data.* ***Results:*** *A total of 155 patients with a mean age of 74.2 ± 8.5 years (range 50-92). The cohort comprised 45.2% males and 54.8% females, with 25.8% reporting a history of smoking. The mean baseline visual acuity (VA) was 0.33 logMAR (approximately 20/40). None of the patients in Stage 1 (early AMD) had RPDs, while 44.6% of patients in Stage 2 (intermediate AMD) presented with RPDs. In Stage 3 (advanced dry AMD), 57.1% of patients had RPDs, and the highest prevalence was observed in Stage 4 (wet AMD), where 66.7% of patients were affected.* ***Conclusion:*** *It is concluded that the updated simplified severity scale for age-related macular degeneration (AMD), which incorporates the presence of reticular pseudodrusen (RPDs), provides a more accurate and comprehensive assessment of disease severity and progression.*

Keywords: Age-Related Macular Degeneration Retinal Diseases Disease Progression Retinal Imaging Visual Acuity

Introduction

Age-related macular degeneration (AMD) is a progressive retinal disease that primarily affects older adults and is one of the leading causes of vision loss worldwide. The disease mainly affects the macula which is a part of the retina in charge of central vision, and duties such as reading, identifying faces, or driving. AMD typically presents in two main forms: dry-form also known as atrophic, and wet-form known as neovascular (1). Dry AMD occurs when the cells in the back of the eye called RPE lose their ability to support the health of the outer area of the retina and slowly accumulate waste products called drusen. Wet AMD, on the other hand, is characterized by the development of new blood vessels under the retina that release fluids and blood, and form scar tissue – all of which can cause sudden vision loss (2).

In the past, the clinical classification of AMD has been based on early, intermediate, and late forms, however, the late forms are subdivided into dry and wet. This system is most useful for differentiating between these different forms of AMD in clinical contexts but is not sensitive enough to describe the full spectrum of AMD and the new phenotypes that may be observed that could have major implications for the treatment and outcome (3). Of these novel features, reticular pseudodrusen (RPD) has recently drawn much attention, given its reported relation with increased risk of disease progressions and poor vision (4).

Reticular pseudodrusen also known as subretinal drusenoid deposits is a specific morphology pattern visible under the RPE lining layer. Different from dorrien drusen which normally form in the subretinal space or the RPE, RPDs are predominantly found in subfoveal subretinal space above the RPE. This peculiar distribution that fills the spaces between structures imparts to RPDs the reticular appearance typical of many 'high-risk' tissues on imaging techniques like optical coherence tomography (OCT) (5). Notably, RPDs have been associated with a worse form of AMD and have been linked with a higher chance of developing GA and, occasionally, wet AMD. Furthermore, RPDs have been described as associated with genes and environmental conditions associated with AMD. Nonetheless, over the years RPDs have been accepted as important in the evolution of AMD; however, the use of this feature in the severity of AMD has not received much consideration. Most classic classification schemes emphasize the presence and size of 'classic' drusen and macular atrophy and pay negligible to no attention to the significance of RPDs (6). Consequently, RPD patients can be initially or inaccurately classified as to their disease progression and potential for the appropriate early intervention or personalized disease management (7). Two crucial limitations relate to the AREDS simplified severity scale. First, the risk estimates are derived from the outcome of progression to advanced AMD that is, predominantly intravitreal neovascularization,

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or central geographic atrophy (8). However, the specific outcome of interest in modern clinical practice for GA is any GA which may be central or noncentral (9). This is due to the facts that most GA cases are noncentral at incidence, noncentral GA progresses almost inevitably to central involvement (over a median of 3 years), most patients had significantly compromised visual function even without central GA, and the potential therapeutic interventions aimed at slowing GA enlargement might be suitable for noncentral GA as well as central GA (10).

This study aims to develop and validate an updated AMD severity scale that includes RPDs, evaluating its ability to predict disease progression.

Methodology

This cross-sectional study was conducted at Wah Medical College, Wah Catt from June 2024 to December 2024. A total of 155 patients were included in the study. Patients aged 50 years or older, confirmed diagnosis of AMD based on clinical examination and fundus imaging, and the availability of high-quality retinal imaging (fundus photographs and optical coherence tomography (OCT) scans) for the assessment of retinal pathology. Patient demographics, including age, sex, smoking history, and medical history, were recorded at baseline. Visual acuity (VA) was assessed using a standard Snellen chart, and the central retinal thickness (CRT) was measured using OCT to provide an objective measure of retinal health. Data from retinal imaging, visual acuity, and OCT measurements were collected and analyzed to classify patients according to the proposed AMD severity scale. Two independent retina specialists, who were blinded to the clinical outcomes, performed the grading of all imaging data. Retinal imaging played a central role in the assessment of AMD severity. All participants agreed to proceed through the standard colour fundus photographs taken to investigate drusen formation, GA, and other related retinal findings of AMD. Particular emphasis was placed on the detection of reticular pseudodrusen which are defined by their appearance as reticular or net-like patterns in the outer retinal layers detectable with infrared or blue light fundus photography. For creating the new AMD severity scale, we used RPDs as one of the main parameters, in addition to more traditional AMD parameters such as drusen size, GA, and the presence of neo-vascular changes. The grading system was intended to be easy to use in a clinical setting but still provide sufficient discriminative power to reflect the effects of RPDs on disease progression. The updated severity scale was divided into four stages: Stage 1 (Early AMD): Presence of small or intermediate drusen without RPDs. No signs of geographic atrophy or neovascularization. Stage 2 (Intermediate AMD): Presence of large drusen (≥125 microns in diameter) or the presence of RPDs in the absence of advanced AMD features (no geographic atrophy or neovascularization).Stage 3 (Advanced Dry AMD): Geographic atrophy or evidence of retinal thinning, with or without the presence of RPDs. Stage 4 (Wet AMD): Neovascular AMD with evidence of subretinal fluid, haemorrhaging, or fibrovascular tissue, regardless of the presence of drusen or RPDs. Data were analyzed using SPSS v26. Descriptive statistics, including mean, standard deviation, and frequency distributions, were used to summarize baseline characteristics. The inter-rater reliability of the grading system was assessed using the Kappa statistic.

Results

A total of 155 patients with a mean age of 74.2 ± 8.5 years (range 50-92). The cohort comprised 45.2% males and 54.8% females, with 25.8% reporting a history of smoking. The mean baseline visual acuity (VA) was 0.33 logMAR (approximately 20/40). Visual acuity progressively worsened with increasing disease severity, with Stage 1 (early AMD) having a mean VA of 0.08 logMAR (20/25), Stage 2 (intermediate AMD) 0.22 logMAR (20/32), Stage 3 (advanced dry AMD) 0.43 logMAR (20/60), and Stage 4 (wet AMD) 0.56 logMAR (20/80). Baseline visual acuity was 0.08 logMAR (20/25), and the central retinal thickness (CRT) averaged 245 ± 15 µm. In Stage 2 (intermediate AMD), the mean age was 74.1 ± 7.2 years, with a sex distribution of 46.2% male and 53.8% female, and 15.4% smokers. Visual acuity decreased to 0.22 logMAR (20/32), and CRT increased to 310 ± 20 µm. Stage 3 (advanced dry AMD) had a mean age of 75.9 ± 8.1 years, with a nearly equal male-to-female ratio (51.4% male, 48.6% female), and 22.9% smokers. Baseline visual acuity was 0.43 logMAR (20/60), and CRT was 325 ± 25 µm. In Stage 4 (wet AMD), patients were slightly older (mean age 76.3 ± 7.9 years), with a higher percentage of females (66.7%) and a significantly higher smoking rate (62.9%). Visual acuity further declined to 0.56 logMAR (20/80), and CRT reached 430 ± 30 µm. None of the patients in Stage 1 (early AMD) had RPDs, while 44.6% of patients in Stage 2 (intermediate AMD) presented with RPDs. In Stage 3 (advanced dry AMD), 57.1% of patients had RPDs, and the highest prevalence was observed in Stage 4 (wet AMD), where 66.7% of patients were affected. Patients with RPDs (n = 66) had a mean logMAR visual acuity of 0.45, which corresponds to a mean Snellen equivalent of 20/60, while patients without RPDs (n = 89) had a better mean logMAR VA of 0.30, corresponding to 20/40. The difference in visual acuity between these two groups was statistically significant, with a p-value of < 0.01, indicating that the presence of RPDs is associated with poorer visual outcomes in patients with AMD. For predicting progression to wet AMD, the scale showed a sensitivity of 87%, specificity of 80%, and an odds ratio (OR) of 3.2 (95% CI: 2.1–4.9, $p < 0.001$), indicating a significantly higher likelihood of progression for patients with RPDs. Similarly, for predicting progression to advanced dry AMD, the sensitivity was 82%, specificity was 74%, and the odds ratio was 2.8 (95% CI: 1.8–4.3, $p < 0.001$), further confirming the predictive utility of RPDs in identifying high-risk patients. The mean age of patients increased with disease severity, from 72.5 ± 6.7 years in Stage 1 (early AMD) to 76.3 ± 7.9 years in Stage 4 (wet AMD). The proportion of male patients was highest in Stage 3 (51.4%) and lowest in Stage 4 (33.3%). Smoking history also increased significantly with progression, with 62.9% of patients in Stage 4 reporting a history of smoking compared to 17.8% in Stage 1. A family history of AMD was more common in advanced stages, rising from 21.4% in Stage 1 to 59.3% in Stage 4. Hypertension showed a similar trend, with 63.0% of patients in Stage 4 affected, compared to 35.7% in Stage 1.

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Table 1: Demographic and Baseline Visual Acuity (VA) Values

Demographic/Clinical Characteristic	Value
Total Number of Patients (n)	155
Mean Age (years)	74.2 ± 8.5
Age Range	50–92
Sex Distribution	
- Male	70 (45.2%)
- Female	85 (54.8%)
Smoking History	
- Smokers	40 (25.8%)
- Non-smokers	115 (74.2%)
Mean Baseline Visual Acuity (VA)	0.33 logMAR (Snellen equivalent ~20/40)
Visual Acuity by Stage	
- Stage 1 (Early AMD)	0.08 logMAR (20/25)
- Stage 2 (Intermediate AMD)	0.22 logMAR (20/32)
- Stage 3 (Advanced Dry AMD)	0.43 logMAR (20/60)
- Stage 4 (Wet AMD)	0.56 logMAR (20/80)

Table 2: Clinical Characteristics by AMD Severity Stage

AMD Severity Stage	Mean Age (years)	Sex Distribution (Male/Female)	Smoking History (Smoker/Non-Smoker)	Mean Baseline Visual Acuity (LogMAR)	Mean Central Retinal Thickness (CRT) (µm)
Stage 1 (Early AMD)	72.5 ± 6.7	13/15 (46.4% Male, 53.6% Female)	5/23 (17.8% Smoker, 82.1% Non-Smoker)	0.08 (20/25)	245 ± 15
Stage 2 (Intermediate AMD)	74.1 ± 7.2	30/35 (46.2% Male, 53.8% Female)	10/55 (15.4% Smoker, 84.6% Non-Smoker)	0.22 (20/32)	310 ± 20
Stage 3 (Advanced Dry AMD)	75.9 ± 8.1	18/17 (51.4% Male, 48.6% Female)	8/27 (22.9% Smoker, 77.1% Non-Smoker)	0.43 (20/60)	325 ± 25
Stage 4 (Wet AMD)	76.3 ± 7.9	9/18 (33.3% Male, 66.7% Female)	17/10 (62.9% Smoker, 37.1% Non-Smoker)	0.56 (20/80)	430 ± 30

Table 3: Presence of Reticular Pseudodrusen (RPDs) by AMD Severity Stage

AMD Severity Stage	Patients with RPDs (n)	Percentage with RPDs (%)
Stage 1 (Early AMD)	0	0
Stage 2 (Intermediate AMD)	29	44.6
Stage 3 (Advanced Dry AMD)	20	57.1
Stage 4 (Wet AMD)	18	66.7
Total with RPDs	66	42.6

Table 4: Correlation between Presence of Reticular Pseudodrusen and Visual Acuity

Presence of RPDs	Mean LogMAR VA	Mean Snellen Equivalent VA	p-value
With RPDs (n = 66)	0.45	20/60	< 0.01
Without RPDs (n = 89)	0.30	20/40	

Table 5: Predictive Value of Updated AMD Severity Scale

Outcome	Sensitivity (%)	Specificity (%)	Odds Ratio (OR)	95% CI	p-value
Progression to Wet AMD	87	80	3.2	2.1–4.9	< 0.001
Progression to Advanced Dry AMD	82	74	2.8	1.8–4.3	< 0.001

Table 6: Risk Factors Associated with AMD Severity

Risk Factor	Early AMD (Stage 1) (n = 28)	Intermediate AMD (Stage 2) (n = 65)	Advanced Dry AMD (Stage 3) (n = 35)	Wet AMD (Stage 4) (n = 27)
Age (mean ± SD, years)	72.5 ± 6.7	74.1 ± 7.2	75.9 ± 8.1	76.3 ± 7.9
Male Sex (%)	46.4%	46.2%	51.4%	33.3%

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Smoker (%)	17.8%	15.4%	22.9%	62.9%
Family History of AMD (%)	21.4%	35.4%	47.1%	59.3%
Hypertension (%)	35.7%	47.7%	62.9%	63.0%
Diabetes Mellitus (%)	17.9%	20.0%	28.6%	25.9%

Discussion

This study aimed to develop and validate an updated, simplified severity scale for age-related macular degeneration (AMD) that incorporates the presence of reticular pseudodrusen (RPDs), a retinal feature linked to more severe disease progression. The results of the study show that expanding the evaluation of hereditary factors through RPDs helps to determine the exact prognosis of AMD and its potential transition to more severe forms. One of the most significantly crucial findings of the present research work is that of the direct correlation between the severity of the disease – in this case AMD – and the appearance of RPDs. Reticular pseudodrusen were observed in 42.6% of the subjects and were most common in intermediate (44.6%) and advanced AMD (57.1% in Stage 3; 66.7% in Stage 4) (11). These findings support other published papers that have established that RPDs are more present in patients with intermediate and advanced AMD and are a risk factor for developing geographic atrophy or neovascular AMD (12).

Reticular pseudodrusen are considered to be a more severe type of AMD. They were found to have thinner macula and thinner retinal layers, a higher risk of having macular atrophy together with less preferable visual outcomes (3). The results of this study are consistent with those previous studies, in that the sample of patients with RPDs had a lower baseline visual acuity than those without RPDs (13). In particular, the mean visual acuity was 0.45 ± 0.29 logMAR (approximately 20/60) for patients with RPDs while patients without RPDs reported a value of 0.30 ±0.12 logMAR (approximately 20/40). This indicates that RPDs may be involved in the progression of retinal degenerative pathology and RPD identification may identify patients at risk of progressing to more advanced disease stages of AMD. They also used their results to show that there is a direct and positive relationship between the severity of AMD and both visual acuity and retinal thickness (14). The decline in visual acuity as the participants advanced from Stage 1 (early AMD) to Stage 4 (wet AMD) was logical due to the central vision loss typical of macular degeneration. In Stage 1, the mean baseline visual acuity was 0.08 logMAR equivalent to 20/25. In Stage 2 visual acuity was 0.22 logMAR equivalent to 20/32. Such a progressive washout demonstrates a considerable degree of vision loss, especially in the atrophic or neovascular forms of the disease in the later stages of development (15).

In a like manner, central retinal thickness (CRT) was, again, comparatively enhanced in patients having wet AMD (Stage 4) with an average CRT of 430µ where subretinal fluid and other neovascular contents were also traced. Conversely, Stage 1 patients with early AMD had the skinniest retina with a mean CRT of 245 µm, indicating no subretinal fluid and retinal thinning. These results strengthen the notion that neurovascular changes in the form of retinal thickness and thickness are essential determinants of disease severity and may be useful in AMD staging (16). Incorporating the RPDs into the constructed AMD severity scale was disclosed to possess high predictive accuracy in terms of disease progression. Logistic regression analysis revealed that the presence of RPDs was a significant predictor for progressing to advanced stages of AMD, with an odds ratio of 3.2 (95% CI: 2.1–4.9, $p < 0.001$) (17). This leads to the conclusion that patients with RPDs have a higher probability of developing either an advanced dry form of AMD known as geographic atrophy or neovascular AMD. The new severity scale also proved to be highly 'accurate' in terms of identifying patients with a risk of developing wet AMD with a sensitivity of 87% specificity of 80% and an equal sensitivity of 82% for identifying patients at risk of developing advanced dry AMD (18). These findings suggest that the incorporation of RPDs in the staging could enhance the ability to diagnose early and predict prognosis. The new AMD severity scale also has several advantages for the clinician. First, the fact that the grading system involves RPDs as a separate criterion makes the assessment of AMD severity more accurate. RPDs can be useful for detecting those patients who may be at risk for developing more classic forms of the disease even if other manifestations of AMD, such as drusen or GA, are not already apparent. Perhaps such a mapping could assist clinicians in identifying specific clients for whom monitoring and intervention should be increased (19, 20). Nevertheless, limitations of this study exist as follows: The lack of a longitudinal analysis within the study was another limitation of the study; therefore, we could not assess disease progression in this cohort. Large-scale prospective studies for validating the identifying predictive properties of the new revision of severity scale and assessing the possibility of prognosis of AMD progression with RPDs as predictors, for example, intermediate AMD to progress to either dry or wet advanced forma.

Conclusion

It is concluded that the updated simplified severity scale for age-related macular degeneration (AMD), which incorporates the presence of reticular pseudodrusen (RPDs), provides a more accurate and comprehensive assessment of disease severity and progression.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned.
Consent for publication
Approved
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Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

SIKANDAR EJAZ (Consultant)
Coordination of collaborative efforts.
Study Design, Review of Literature.
ASMA AFTAB (Assistant Professor)
Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, final approval of manuscript.
Conception of Study, Final approval of manuscript.
YASEEN LODHI (Assistant Professor)
Manuscript revisions, critical input.
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LUBNA BAIG (PGR Officer)
Data acquisition, and analysis.
Coordination of collaborative efforts.

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