Salud, Ciencia y Tecnología. 2025; 5:544
doi: 10.56294/saludcyt2025544

ORIGINAL

Development and Validation of the Asian AMD Age-Related Macular Degeneration Risk Scale

Desarrollo y validación de la escala asiática de riesgo de degeneración macular asociada a la edad AMD

Inara Ismayilova[1], Andrii Korol[2], Neilya Aldasheva[3]

[1]Department of Public Health, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan.
[2]Division of Research of Laser Biologic Action and Application in Ophthalmology, State Institution "THE Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine", Odesa, Ukraine.
[3]Department of Ophthalmology, Kazakh Eye Research Institute. Almaty, Kazakhstan.

Cite as: Ismayilova I, Korol A, Aldasheva N. Development and Validation of the Asian AMD Age-Related Macular Degeneration Risk Scale. Salud, Ciencia y Tecnología. 2025; 5:544. https://doi.org/10.56294/saludcyt2025544

Submitted: 17-02-2024 **Revised:** 23-06-2024 **Accepted:** 29-10-2024 **Published:** 01-01-2025

Editor: Prof. Dr. William Castillo González

Corresponding author: Inara Ismayilova

ABSTRACT

Introduction: this study aimed to develop a method for predicting the risk of developing macular degeneration in the early stages by facilitating prompt intervention by medical professionals.
Method: using a cross-sectional design, 455 age-related macular degeneration (AMD) patients from Kazakhstan were recruited via random sampling. Demographic traits, familial AMD history, medical history, and eye-related characteristics were collected through a systematic questionnaire. The patient cohort comprised 169 Caucasians and 286 Asians, with 160 males and 295 females.
Results: notably, 117 individuals (25,7 %) were classified as high AMD risk, 322 (70,8 %) as moderate risk, and 16 (3,5 %) as low risk. Additionally, eye-related findings revealed high-risk factors, including bright iris colors, increased UV exposure, and cataract surgery, alongside presbyopia and myopia. The study underscores the need for national/regional AMD risk stratification to inform monitoring and screening programs. Recognizing high-risk individuals holds paramount significance from both public health and therapeutic perspectives, offering opportunities for early detection and management to mitigate permanent vision loss.
Conclusions: the findings elucidate the interplay between risk factors, shedding light on their collective impact on AMD risk. Overall, this study's predictive model and risk categorization framework have substantial implications for ophthalmological practice, enabling timely preventive measures and potentially revolutionizing AMD management.

Keywords: Macular Degeneration; Eye Diseases; Risk Factors; Perceived Social Support.

RESUMEN

Introducción: este estudio tenía como objetivo desarrollar un método para predecir el riesgo de desarrollar degeneración macular en las primeras etapas facilitando la pronta intervención de los profesionales médicos.
Método: utilizando un diseño transversal, se reclutaron 455 pacientes de degeneración macular asociada a la edad (DMAE) de Kazajstán mediante muestreo aleatorio. Mediante un cuestionario sistemático se recogieron datos demográficos, antecedentes familiares de DMAE, historia clínica y características oculares. La cohorte de pacientes comprendía 169 caucásicos y 286 asiáticos, con 160 varones y 295 mujeres.
Resultados: en particular, 117 individuos (25,7 %) se clasificaron como de alto riesgo de DMAE, 322 (70,8 %) como de riesgo moderado y 16 (3,5 %) como de bajo riesgo. Además, los hallazgos relacionados con los ojos revelaron

factores de alto riesgo, como los colores brillantes del iris, el aumento de la exposición a los rayos UV y la cirugía de cataratas, junto con la presbicia y la miopía. El estudio subraya la necesidad de una estratificación nacional/regional del riesgo de DMAE que sirva de base a los programas de seguimiento y cribado. Reconocer a los individuos de alto riesgo tiene una importancia primordial tanto desde el punto de vista de la salud pública como desde el punto de vista terapéutico, ya que ofrece oportunidades de detección precoz y tratamiento para mitigar la pérdida permanente de visión.

Conclusiones: los hallazgos dilucidan la interacción entre los factores de riesgo, arrojando luz sobre su impacto colectivo en el riesgo de DMAE. En general, el modelo predictivo de este estudio y el marco de categorización del riesgo tienen implicaciones sustanciales para la práctica oftalmológica, permitiendo la adopción de medidas preventivas oportunas y revolucionando potencialmente la gestión de la DMAE.

Palabras clave: Degeneración Macular; Enfermedades Oculares; Factores de Riesgo; Apoyo Social Percibido.

INTRODUCTION

Research Problem

In persons over 60, age-related macular degeneration (AMD) is one of the leading causes of blindness in the globe.[1] Recent research in Europe indicated that the incidence of early AMD increased from 3,5 % in people aged 55-59 years to 17,6 % in those aged 85 and older, and that the prevalence of late AMD increased from 0,1 % to 9,8 %, respectively.[2] All these changes might lead to a nearly doubling of the number of afflicted people by 2040, with early AMD affecting between 14,9 and 21,5 million people and late AMD affecting between 3,9 and 4,8 million people.[2]

Research Focus

Early AMD is characterised by common disturbances including diminished reading ability and modest central distortion. Other symptoms that might manifest include central scotoma and trouble recognising faces. The majority of people are asymptomatic at this time, which should be noted. A neovascular type of late AMD develops to an abrupt impairment in vision, but the nonneovascular variant may be characterised by a slow, progressive loss of central vision function. AMD significantly lowers patients' quality of life by impairing their everyday functioning and eyesight. However, choriocapillaris, the retinal pigment epithelium (RPE), Bruch's membrane, and the photoreceptors are the four associated tissues that exhibit the most significant abnormalities in AMD's pathogenesis.[3] An essential stage in the molecular pathways leading to clinically relevant AMD alterations is the impedance of RPE cell activity.[3] RPE degradation leads to irreversible photoreceptor degeneration.[3] Between RPE and Bruch's membrane, yellowish drusen deposits that are protein- and lipid-rich build up.[4,5,6] Additionally, there are four basic processes that lead to the development of the two forms of AMD: wet (neovascular, exudative) and dry (geographic atrophy, non-exudative). These processes include lipofuscinogenesis, drusogenesis, inflammation, and neovascularization.[3]

For AMD, new and efficient therapies have been developed. According to reports, serous pigment epithelial detachment associated with AMD can be effectively treated with subtenon and intravitreal triamcinolone acetonide to preserve the retina's anatomical structure.[7] While 577-nm micropulse retinal pigment epithelium laser photocoagulation was discovered to be an efficient and secure therapy for patients with age-related maculopathy, including those with drusenoid pigment epithelial detachment and a wide variety of morphological and functional deficits.[8] Another study found that comprehensive treatment for age-related maculopathy and dry AMD (a course of laser stimulation of the retina followed by oral supplementation with carotenoids, lutein and zeaxanthin) improved visual function, reduced anxiety and depression, and significantly improved quality of life at the 6-month time-point. Additionally, it is crucial to let patients know about routine ophthalmological examinations in order to early diagnosis and treatment of degenerative eye diseases.[9] Early detection of those most at risk of developing neovascular AMD is strongly recommended since prompt treatment when it first manifests will improve visual results.[10,11,12,13,14,15] In order to educate patients and implement preventive measures like vitamin supplementation to delay the advancement of the disease, it is critical to quickly identify those patients who are at risk.[16,17,18,19] Consequently, identifying high-risk individuals is essential for conserving vision.

Currently, color fundus images are used to manually assess the extent of drusen, the characteristic early and intermediate AMD subretinal deposits that are yellowish white in color as well as other retinal changes like abnormalities in the retinal pigment.[20] Ethnic and racial variations in the prevalence of AMD have been discovered in several population-based research, with early AMD being more frequent in Europe than Asia but late AMD being equally prevalent on these continents.[21] Smoking is the major risk factor that may be changed to prevent the development of progressive AMD; smokers have a 2-4 times higher chance of developing AMD.[22]

Age over 65, heritage from Northern Europe, and family history are risk factors for advanced AMD that cannot be changed.[23] Furthermore, AMD in one eye raises the possibility that AMD may manifest itself in the adjacent eye. In general, the rates of AMD in men and women are comparable.[24]

Among risk assessment methods, simplified Thea AMD Risk-Assessment Scale (STARS) is a simple, new self-assessed questionnaire showing good perception of risk for AMD in two large European samples.[25] Similar, Kulik and Bogomolov[26] developed a method for predicting the risk of developing macular degeneration. Whereas, development risk questionnaire was developed by Rizaev, Yangieva.[27] Ophthalmologists may use it in ordinary clinical practise or as a tool for the general public to self-evaluate their risk of AMD. However, none of these questionnaires are completely suitable for assessing the risk factors for AMD in Kazakhstan due to the geographical location and national characteristics. Therefore, authors decided to develop their own method for predicting risk factors for the development of AMD in Kazakhstan.

So, the current study aimed to develop a method for predicting the risk of developing macular degeneration in the early stages with levels of evidence that can be swiftly assessed by physicians or ophthalmologists in order to implement preventative measures or alter current practices.

METHOD

Research plan and sample

A cross-sectional descriptive design with simple random sampling was employed in this research. Data were collected from 573 AMD patients across eye clinics in three major cities in Kazakhstan, including the Medical Centre of the Administration of the President of the Republic of Kazakhstan's Nur Sultan Hospital, Mediker Clinic in Shymkent, Raevskyi Laser Center in Almaty, and the Kazakhstan Research Institute of Eye Diseases in Almaty. Random invitations were sent to all AMD patients to take part in the trial. Patients who provided consent and satisfied the inclusion requirements were enrolled in the trial. Age more than 30 and AMD stage 2-4, as determined by the Age-Related Eye Disease Study (AREDS) staging system,[28] were the inclusion criteria. A willingness to engage, fluency in Russian or Kazakh, and the ability to speak and comprehend those languages.

The study was given permission by the Kazakh Medical University of Continuing Education and Asfendiyarov Kazakh National Medical Universit's regional ethics committees in line with the principles of the Helsinki Declaration. Each participant completed an informed consent form after hearing about the specifics of the study.

Instruments for evaluation

A questionnaire was developed based on the Asian AMD Risk Scale, for which a copyright certificate was obtained, identified as No. 119838, dated 19 June 2023. The information was gathered using our own developed questionnaire in four major categories: demographics (gender, race and age); personal medical history (smoking; myocardial infarction, BMI, arteriosclerosis, hypercholesterolemia); family history of AMD; and eye-related parameters (refractive errors, cataracts, iris color, UV insolation).[25] Further, the patients were divided into three groups as follows; low risk (0-10), intermediate risk (11-20), and high risk (>21).

Statistical analysis

The calculation of descriptive statistics served to depict the independent variables. For continuous data, mean and standard deviation were given; for categorical data, frequency and percentage were given. The final age categorization was established using the age cluster analysis. Coefficient indicators were determined for each of the 14 questions. A rich logistic regression analysis was performed to determine the relationship of risk factors with AMD. External validation including specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), negative diagnostic likelihood ratio (DLR-) and positive diagnostic likelihood ratio (DLR+) was done. The data was analyzed using SPSS version 25.0 for Windows.

RESULTS

Population characteristics

Among 573 patients approaching, 455 patients were included finally. Data was missing from one hundred and eighteen patients and were not included finally. The age group clustering is determined by Hierarchical clustering using SPSS, it recommended 6 clusters. The age groups you made in the revised file seem ok. The minimum age is 35 and the maximum age is 93. There is a total of 57 age groups which are divided into 6 groups as per hierarchical clustering.

Response rates

The descriptive characteristics of the sample are shown in Table 1 where coefficients / scores are assigned to the patient according to their answers. Based on these scores, the total score was calculated and its correspondence to the low / medium / high risk group for developing AMD. The study sample consisted of 169

(37,1 %) Caucasian and 286 (62,9 %) Asian patients, with 160 (35,2 %) male and 295 (64,8 %) female patients. Maximum patients (n=120) were in the age group 61-70 years, while the lowers percent (2,0 %) were from age group up to 40 years. The family history of AMD was present in 100 (22,0 %) patients. Personal medical history parameters showed that the maximum patients (n=211) were from groups having BMI< 25 followed by group having BMI between 25-30 (n=183). Most of the patients were never smokers (n=303) followed by current smokers (n=144) and former smokers (n=8). There were 309 (67,9 %) patients' history of Arterial hypertension, while 96 (21,1 %) patients were having a history of Myocardial infarction. 128 (28,1 %) patients have a history of hypercholesterolemia, and 115 (25,3 %) patients had a history of Atherosclerosis. Eye-related parameters showed that 183 patients had cataract surgery, 245 patients had light iris color, and 237 patients were in conditions of increased UV insolation. The percentage of light eyes (iris color) was higher than dark ones. There were 141 patients with myopia and 208 patients with presbiopsiya (table 1).

Table 1. Response rates corresponded to the developed AMD risk scale

Sr. No.	Variables	Category	Coefficient / score	Frequency (%)
1.	Gender	Male	0	160 (35,2 %)
		Female	1	295 (64,8 %)
2.	Age	up to 40	0	9 (2,0 %)
		41-50	1	43 (9,5 %)
		51-60	2	83 (18,2 %)
		61-70	3	120 (26,4 %)
		71-80	4	107 (23,5 %)
		above 80	5	93 (20,4 %)
3.	Race	Caucasian	0	169 (37,1 %)
		Asian	3	286 (62,9 %)
4.	Family history of AMD (siblings, parents)	No	0	355 (78,0 %)
		YES	7	100 (22,0 %)
5.	BMI (kg)	BMI< 25	0	211 (46,4 %)
		BMI between 25-30	1	183 (40,2 %)
		BMI> 30	2	61 (13,4 %)
6.	Smoking	Never smoked	0	303 (66,6 %)
		Former smoker (interrupted for over 10 years)	1	8 (1,8 %)
		Current smoker	2	144 (31,6 %)
7.	History of Arterial hypertension	No	0	146 (32,1 %)
		YES	3	309 (67,9 %)
8.	History of Myocardial infarction	No	0	359 (78,9 %)
		YES	3	96 (21,1 %)
9.	History of hypercholesterolemia	No	0	327 (71,9 %)
		YES	2	128 (28,1 %)
10.	History of Atherosclerosis	No	0	340 (74,7 %)
		YES	4	115 (25,3 %)
11.	Cataract surgery	No	0	272 (59,8 %)
		YES	5	183 (40,2 %)
12.	Refractive errors	Normal	0	106 (23,3 %)
		Myopia	2	141 (31,0 %)
		Presbiopsiya	5	208 (45,7 %)
13.	Iris color	Dark	0	210 (46,2 %)
		Light	1	245 (53,8 %)
14.	UV insolation	No	0	218 (47,9 %)
		YES	1	237 (52,1 %)

Risk Factors

The results showed that 16 (3,5 %) patients were classified as low risk, 322 (70,8 %) as moderate risk and 117 (25,7 %) as high-risk group for AMD (table 2).

The external validation parameters showed 100 % sensitivity, specificity, PPV, NPV, accuracy, and 0 % value for DLR+ and DLR- as presented in table 3.

https://doi.org/10.56294/saludcyt2025544

Table 2. Classification by groups of risk factors corresponds to the diagnosis

Risk Groups	Frequency	Percent	Valid Percent	Cumulative Percent
Low risk for AMD	16	3,5	3,5	3,5
Moderate risk for AMD	322	70,8	70,8	74,3
High risk for AMD	117	25,7	25,7	100,0
Total	455	100,0	100,0	

Table 3. Re-verification of the prognostic function (external validation)

Validation parameters	%
Specificity	100
Accuracy	100
Sensitivity	100
PPV	100
NPV	100
DLR+	0
DLR-	0

Receiver operator characteristic (ROC) curve for different parameters have been presented in figure 1.

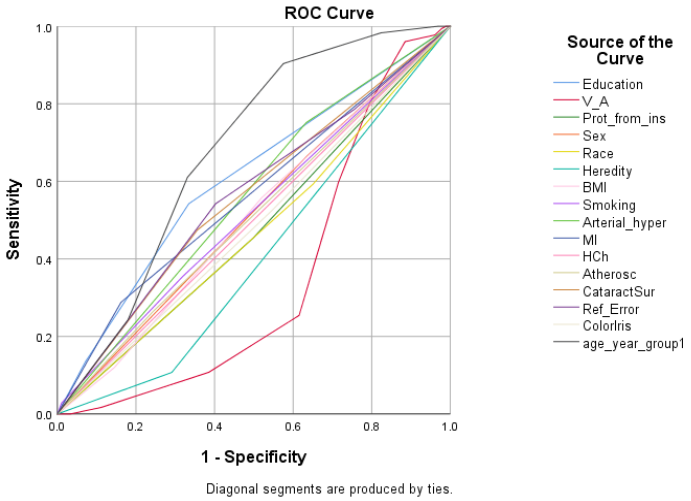

Figure 1. ROC curve for patients with AMD

Significant correlations between the demographic information, family history of AMD, personal medical history, and eye-related characteristics were shown by the rich logistic regression analysis (table 4).

Table 4. A thorough logistic regression study to ascertain how risk variables relate to AMD

Model/Parameters	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	0,339	0,072		4,723	0,000
Sex	0,105	0,037	0,079	2,829	0,005
Age	0,140	0,012	0,293	11,424	0,000
Race	0,086	0,008	0,330	10,590	0,000
Heredity/family history	-0,015	0,006	-0,068	-2,594	0,010
BMI	0,085	0,023	0,095	3,686	0,000
Smoking	0,095	0,018	0,147	5,309	0,000

https://doi.org/10.56294/saludcyt2025544

Arterial hypertension	0,116	0,012	0,257	9,595	0,000
Myocardial infarction	0,090	0,014	0,176	6,483	0,000
Hypercholesterolemia	0,097	0,027	0,139	3,591	0,000
Atherosclerosis	0,080	0,014	0,221	5,598	0,000
Cataract surgery	0,094	0,007	0,366	14,242	0,000
Reflective error	0,102	0,008	0,332	13,248	0,000
Color of Iris	-0,011	0,038	-0,009	-0,291	0,771

DISCUSSION

According to Colijn, Buitendijk,[2] AMD is a prevalent cause of visual loss in the ageing population. From the early and intermediate stages of AMD, which have minimal or moderate visual anomalies, to its late stage, when the rapid loss of central vision might occur. From a public health and therapeutic standpoint, it is critical to identify people who are at high risk of developing late AMD, especially neovascular AMD, since this would enable earlier identification of the illness and more effective treatment. According to recent studies, Patients with intermediate AMD are more likely to acquire advanced AMD.[29] In the current study, a questionnaire was developed based on the Asian AMD Risk Scale. The findings of our study reported age and smoking as significant factors that contributed to AMD. Maximum patients (n=120) were in age group 61-70 years, while the lowers percent (2,0 %) were from age group up to 40 years. Whereas most of the patients were never smokers (n=303) followed by current smokers (n=144) and former smokers (n=8). These findings are inconsistent with the reported studies where two risk factors that have been connected to AMD include age and smoking.[30,31,32,33,34,35,36] The literature also supported our results as strong and persistent correlations with growing older, smoking now, having had cataract surgery before, and having a family history of AMD were found in a meta-analysis.[37] In the current study, the maximum number of patients (n=211) were from groups having BMI< 25 followed by group having BMI between 25-30 (n=183) and there were significant correlations of BMI (P=0,000) with AMD. Similar to our findings, previously conducted studies reported that greater BMI with a history of cardiovascular disease increased fibrinogen levels, and hypertension and were all tangentially associated with AMD. Total blood cholesterol was shown to be negatively correlated with the development of early AMD in people of European ancestry, although associations between variations in cholesterol levels and AMD have been less oftenestablished.[1,38] These findings support our results which reported 28,1 % patients with the history of hypercholesterolemia and 25,3 % patients with the history of atherosclerosis.

According to the findings of the current study among patients, 25,7 % were at a high risk of getting AMD, 70,8 % had a moderate risk, and 3,5 % had a low risk. These findings concur with those of published studies on cohorts from France and Italy.[25] According to our findings, the majority of patients (n=120) were between the ages of 61 and 70, while the minority of patients (2,0 %) were between the ages of 40 and 60. Numerous research in literature supports our findings.[1,21,39,40,41,42]

Our findings also showed that 22,0 % of the patients have a family history of AMD. These findings are in accordance with the previous study which reported that siblings of persons with AMD have a three to six times higher chance of getting the condition compared to the general population.[43] Additionally, the Al-Khobar study found a similar relationship between family history and AMD incidence.[39] Smith and Mitchell [44] found a substantial correlation between wet AMD patients and family history, with the link being stronger overall. In a similar vein, [45] identified a statistically significant connection between genetic background and AMD in a population-based cohort from the ALIENOR research with a four-year follow-up. Due to genetic susceptibility to the condition, the majority of research has demonstrated a favourable correlation with family history.[22] The rest not only did not have a history of heredity but also were those who did not know about the diseases of their grandparents.

Additionally, according to our findings, the majority of patients (n=303) did not smoke, followed by current smokers (n=144), and past smokers (n=8) because of the mentality is that women rarely smoke, so the rate of non-smokers is higher. However, prior research shown that smokers are more likely than non-smokers to acquire AMD.[46,47,48] The risk of AMD in ex-smokers was subsequently studied in 11 trials, which were categorised by Thornton, Edwards.[46] Comparing all of them to never-smokers, they all had a modestly elevated risk of developing AMD.[46] However, the risk magnitude for former smokers was never greater than that for present smokers. Some data indicate that it takes more than 20 years to “wash-out” and enter a comparable hazard zone.[47] Additionally, it has been demonstrated that smoking habits and the likelihood of getting AMD were related.[49,50] Smoking is believed to cause degenerative changes in the macula, increased ischemia, hypoxia, and decreased choroidal blood flow.[51]

Rotterdam Study is one of many studies that found a strong link between smoking and AMD.[37,39,52,53,54,55] This link revealed that smokers and ex-smokers advanced AMD more quickly than non-smokers in younger age groups

(85 years) than non-smokers.[53,54] A cohort study discovered that there is a possibility for a four- to six-fold increase in disease progression and that those who never smoked had a higher likelihood of having regression than present and past smokers.[55] But the population-based SHIP-Trend analysis refuted a strong connection to smoking.[56] The carcinogens in cigarettes are hypothesized to have a role in the pathological development of AMD by increasing oxidative stress. Numerous research has shown that smoking may pose a danger as a result.[22]

An additional observation in our study is the higher percentage of patients with light eye colour (53,8 %) compared to dark eye colour (46,2 %), which is consistent with emerging research indicating a possible link between eye colour and susceptibility to age-related macular degeneration (AMD). This phenotypic trait may intersect with genetic predispositions, providing further context for targeted public health strategies and individualized therapeutic approaches for AMD prevention in specific demographic groups. Further research is required to substantiate the relevance of eye colour as an AMD risk factor and its potential interactions with established predictors such as age and smoking status.

The results of our study showed that there were 67,9 % patients with the history of arterial hypertension. This finding is also evident from several research that greater blood pressure and the onset of AMD are significantly linked.[34,37,57,58] These results also support the findings of our study (p = 0,000). A limited number of studies, meanwhile, failed to detect a link between high blood pressure and the development of AMD.[1,58,59] Age-related factors such as AMD and hypertension make our study's findings scientifically conceivable. According to a study by Wang, Klein,[60] the chance of progressive AMD at the 5-year visit rose by up to ten times after cataract surgery. However, according to our data, people who have had cataract surgery are more likely to develop AMD.

CONCLUSIONS

In conclusion, the creation of national or regional stratification of the population according to the risk for AMD may represent a crucial step in developing monitoring guidelines and screening programmes. The current study validated a risk assessment method using the newly developed Asian AMD Risk Scale to detect AMD in its early stages among patients in Kazakhstan, taking into account their geographical location and national characteristics. The findings regarding the interrelationship between risk variables may contribute to a clearer understanding of the role each risk factor plays in the overall risk of AMD, improving the positioning of each risk factor within this context. Assumptions may be made regarding the logic and ethics of establishing monitoring or screening programmes for eligible patients. However, the increasing number of individuals affected by AMD warrants attention and action. It remains ethically justifiable to consider such procedures or programmes, even in the absence of viable treatment for dry AMD, as they may facilitate regular monitoring, provide ongoing education on avoiding risk factors, and disseminate information on the benefits of AREDS. It is also necessary to conduct a survey in an earlier group of the population to identify groups / patients who have a high risk of developing AMD. Since this leads to early disability. Accordingly, it will reduce the state's expenses for treatment.

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FINANCING

The authors did not receive financing for the development of this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Inara Ismayilova, Andrii Korol.
Data curation: Neilya Aldasheva.
Formal analysis: Andrii Korol.
Research: Inara Ismayilova.
Methodology: Neilya Aldasheva.
Project management: Andrii Korol.
Resources: Neilya Aldasheva.
Software: Andrii Korol.
Supervision: Inara Ismayilova.
Validation: Neilya Aldasheva, Andrii Korol.
Visualization: Inara Ismayilova.
Writing - original draft: Andrii Korol, Neilya Aldasheva.
Writing - proofreading and editing: Inara Ismayilova.