A Computational Tool Supporting the Diagnosis of Age-Related Macular Degeneration

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***Abstract*—This work describes a diagnostic graphical tool (classification maps) recently developed and published by the authors to support the detection of Age-Related Macular Degeneration (AMD). These maps, constructed using an ordinal regression model, visually represent the progression of AMD. In this model, the degree of AMD advancement serves as the ordinal dependent variable. Independent variables, such as Central Retinal Thickness (CRT), Ganglion Cell Complex thickness (GCC), Macular Pigment Optical Density (MPOD), Early Treatment Diabetic Retinopathy Study (ETDRS) scores, Snellen visual acuity, and patient age are incorporated into the analysis and displayed on the axes of the maps.**

Keywords–medical informatics; biostatistics; mathematical modeling

I. INTRODUCTION

Central vision loss caused by Age-Related Macular Degeneration (AMD) is a significant global health concern, particularly among individuals over 60 years of age. AMD accounts for nearly 50% of cases of blindness as defined by legal standards [1] [2]. This chronic, progressive condition affects the outer layers of the central retina and the choroid. The prevalence of AMD is expected to grow due to increasing life expectancy and heightened exposure to risk factors contributing to degenerative changes in the macula [1] [3].

In the United States, approximately 8 million individuals are diagnosed with early AMD, and more than 1 million are predicted to develop advanced AMD within the next five years [2]. By 2050, one in ten Americans over the age of 50 is projected to have AMD [3]. In Poland, an estimated 1.5 million people suffer from macular degeneration, including 130000 cases of the more severe exudative form of AMD [4]. Globally, the number of AMD cases is expected to rise from 196 million in 2020 to 288 million by 2040 [5]. Europe currently has the highest AMD incidence, with future case numbers anticipated to be surpassed only by Asia [6]. AMD prevalence rates vary across regions, with 12.33% in Europe, 7.38% in Asia, and 7.53% in Africa [5] [6].

The risk of AMD increases with age. Among individuals aged 60 and older, 13.4% are affected, compared to 2.8% among those aged 40–59. Advanced AMD is present in 1.4% of individuals at age 70, increasing to 5.6% at age 80, and 20% at age 90 [7]. The study of AMD has deep historical roots. The advent of ophthalmoscopy, the examination of the eye's fundus, marked the beginning of modern retinology. Hermann von Helmholtz's invention of the ophthalmoscope in 1851 was a pivotal milestone. The macula was first identified in detail in the late 18th century by Samuel Thomas Soemmerring, who described the yellowish area in the posterior retina. In 1875, Jonathan Hutchinson and Warren Tay documented symmetrical fundus changes, later classified as "senile macular degeneration" by Otto Haab in 1885 [8].

While progress in AMD research was initially gradual, it focused on identifying risk factors and developing early classifications. A major advancement occurred in 1967 when J. Donald Gass from Florida described the pathogenesis of central vision loss and delineated the stages of AMD progression [9] [10].

In this work, we review a new computational method, recently developed and published by us [11], for supporting the detection of AMD. Details of this method are outlined in Section II, whereas Section III provides a summary and discusses our future plans.

II. METHOD AND RESULTS

The study involved the examination of 132 eyes from 66 patients, classified according to AMD progression using the four-point Age-Related Eye Disease Scale (AREDS) [12]. As the most widely utilized system for categorizing AMD, the AREDS scale divides AMD progression into the following stages:

1) AREDS 1 (control group): Absence of AMD or presence of only a few small drusen ($< 63\mu m$ in diameter).
2) AREDS 2: Early AMD, characterized by numerous small drusen ($> 15\mu m$), several intermediate-sized drusen ($63 - 125\mu m$), or Retinal Pigment Epithelium (RPE) abnormalities, such as increased pigmentation or depigmentation.
3) AREDS 3: Intermediate AMD, including numerous medium-sized drusen, at least one large druse ($> 125\mu m$), or geographic atrophy not involving the central macula.
4) AREDS 4: Advanced AMD, involving geographic atrophy of the RPE affecting the macula or neovascular maculopathy. This includes Choroidal Neovascularization (CNV), serous or hemorrhagic retinal

or RPE detachment, exudates and hard fibrovascular proliferations beneath the retina and RPE, and discoid scars (choroidal fibrosis) [13] [14].

Of the examined eyes, 32 were classified as AREDS 1, showing no AMD features and serving as the control group due to the absence of visible fundus changes. The remaining eyes were distributed among the AREDS 2 (37 eyes), AREDS 3 (33 eyes), and AREDS 4 (30 eyes) groups.

In certain patients, AMD-related changes were present in only one eye, or the severity varied between eyes, as determined by the AREDS classification.

Outpatient examinations were conducted in 2016–2017 at the Ophthalmology Clinic of UCK in Gdańsk, Poland. Diagnoses were established following the standards and recommendations of the Polish Society of Ophthalmology, consistent with the American Academy of Ophthalmology (AAO) guidelines [15]. Data regarding disease stage and overall health were gathered through medical history, the Simplified Théa AMD Risk-assessment Scale (STARS), resting blood pressure and pulse measurements, and detailed ophthalmological assessments. These assessments included Spectral Optical Coherence Tomography (SOCT) macula scans and Macular Pigment Optical Density (MPOD) measurements. Patients were fully informed about the tests conducted.

Inclusion criteria for the AMD and control groups were an age of over 55 years and an AMD diagnosis aligned with the AREDS scale and Polish Society of Ophthalmology guidelines.

Statistical analyses were conducted using the R programming language [16]. Quantitative variables were summarized using median, minimum, and maximum values. The Kruskal-Wallis test was applied to compare variables across AMD advancement groups, with post-hoc tests following significant results.

Ordinal regression, implemented via a generalized linear model, was utilized to predict ordinal variables, where only relative ordering is important. The dependent variable was the AMD advancement level. Independent variables included Central Retinal Thickness (CRT), average Ganglion Cell Complex (GCC) thickness, MPOD, ETDRS visual acuity, Snellen visual acuity, and patient age. Measurements were performed using the Zeiss Cirrus HD-OCT model 400.

Logit functions were used in the analysis. Since, in this case, the maximization of probability (or the logarithm of probability) does not have an analytical solution, the iteratively reweighted least squares (IRLS) technique was employed to estimate the regression coefficients. The models included all the collected values for each variable. The quality of the models was assessed by evaluating the statistical significance of the coefficients, the -2 log-likelihood value, and the frequency of correctly predicted categories based on the values of the independent variables.

This modeling resulted in a tool for estimating AMD progression. Due to the limited sample size, models were restricted to pairs of independent variables. The article highlights pairs of variables with statistically significant regression coefficients, alongside their Odds Ratios (OR), Confidence Intervals (CI), and thresholds for ordinal categories.

The statistical significance level was set at $\alpha = 0.05$.

Using the proposed model, classification maps were generated, serving as a graphical tool to support the diagnosis of AMD [11]. These maps enable the classification of patients' eyes into specific groups (control group, AREDS 2, AREDS 3, or AREDS 4) based on the values of variables represented on their axes. Classification maps, based on these models, visually represent the predicted probabilities for each AMD stage, using a color-coded scheme. This alternative computational approach facilitates the accurate diagnosis of all stages of AMD with high or good precision.

III. Conclusion

The method described enables the classification of a patient's eyes into specific stages of AMD. The variable pairs displayed on the map axes serve as diagnostic markers essential for determining the stage of AMD.

In our future work, we plan to adapt this method to describe other diseases, such as dementia severity, degrees of obesity, and more.

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