Can CHADS2 and CHA2DS2-VASc Scores be Used to Predict Clinical Outcomes in Patients with Age-Related Macular Degeneration?

Erdinc Bozkurt[1], Ersin Muhafiz[2], Şerif Nizamoğulları[3], İbrahim Rencüzoğulları[4]

ABSTRACT

Purpose: To evaluate the usability of CHADS2 and CHA2DS2-VASc scores in clinical practice for age-related macular degeneration (AMD) and their effects on treatment prognosis in wet-type AMD.

Materials and Methods: Ninety patients with dry-type AMD aged 65-90 years, 115 patients with wet-type AMD, and 90 controls without any retinal disease were included in the study. Best-corrected visual acuity (BCVA) values and previously administered intravitreal anti-VEGF injection (IVI) treatments were recorded. The ejection fractions of the patients were measured and evaluated for the diagnosis of congestive heart failure (CHF). The presence of diabetes mellitus (DM), hypertension (HT), history of stroke, and vascular diseases (VD) was questioned.

Results: A significant difference was observed between the AMD groups only in terms of DM and VD (p=0.032 and 0.011, respectively). There was also a significant difference between the groups in terms of CHADS2 and CHA2DS2-VASc scores, but these two scoring systems were not superior to each other in ROC analysis.

When the wet-type AMD cases were compared according to the number of injections, there was a significant difference in terms of CHF, DM, stroke, and VD. (p=0.001, 0.01, 0.02, and 0.01, respectively). When the treatment groups were compared in terms of the CHADS2 and CHA2DS2-VASc scores, a statistically significant difference was found (p=0.01 and 0.05, respectively), and as the number of intravitreal injections required for treatment increased, the score increased for both systems.

Conclusions: CHADS2 and CHADS2-VASC clinical scoring systems can be predictors of AMD. They can also indicate the numbers of injections needed for treatment.

Keywords: AMD, risk factors, CHADS2, CHA2DS2-VASc.

INTRODUCTION

Age-related macular degeneration (AMD) was first described by Otto Haab in 1885 as a macular pathology progressing with pigmentation change and atrophy.[1] It progresses with the degeneration of photoreceptors, retinal pigment epithelium, Bruch's membrane, and choriocapillaris in the macula region. It is known as the most common cause of central vision loss in people aged 65 years and older in developed countries. It is seen with a frequency of 10% between the ages of 65-75 years, and 25% over the age of 75.[2] Classically, AMD is divided into two main subgroups: dry type resulting in progressive degeneration and chorioretinal atrophy of the retinal pigment epithelium and photoreceptors and wet (exudative) type characterized by choroidal neovascularization and bleeding targeting the subretinal area.[3]

According to the Age-Related Eye Disease Study (AREDS), dry-type AMD is defined as the presence of early-middle stage and geographic atrophy and constitutes 85-90% of AMD cases. Advanced-stage AMD, known as stage 4, is also referred to as neovascular/exudative/wet type and constitutes 10-15% of all AMD patients.[4-5] Although it is known that hemodynamic changes, macular hypoperfusion, and oxidative stress play an important role in the pathogenesis of AMD, this has not yet been fully elucidated and the etiology of the disease is considered to be multifactorial.[6]

1- Ophthalmologist, MD, University of Health Sciences, Umraniye Training and research Hospital, Ophthalmology Department, Istanbul, Turkey

2- Associate Professor, MD, Kafkas University Faculty of Medicine, Ophthalmology Department, Kars, Turkey

3- Assistant Dr, MD, Kafkas University Faculty of Medicine, Ophthalmology Department, Kars, Turkey

4- Associate Professor, MD, Kafkas University Faculty of Medicine, Cardiology Department, Kars Turkey

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Correspondence Adress:
Erdinç Bozkurt
University of Health Sciences, Umraniye Training and research Hospital, Ophthalmology Department, Istanbul, Turkey

Phone: +90 506 615 7788
E-mail: drerdincbozkurt@hotmail.com

CHADS2 and CHA2DS2-VASc are the currently used scoring systems used to determine the risk of thromboembolism in patients with atrial fibrillation (AF). According to the CHADS2 scoring system, the presence of congestive heart failure (CHF), hypertension (HT), advanced age, diabetes mellitus (DM), and stroke history is given 1 point each.[7-8] CHA2DS2-VASc risk score is calculated by giving 1 point each for the presence of CHF (ejection fraction <40%), HT, age of 65-74 years, diabetes mellitus, vascular disease (myocardial infarction or peripheral artery disease) and 2 points each for a stroke or transient ischemic attack (TIA), and age > 75 years.[9]

The aim of the study was to show the importance of CHADS2 and CHA2DS2-VASc scores in dry-type and wet-type AMD and to investigate the effects of these scoring systems on the treatment prognosis of wet-type AMD.

MATERIAL- METHOD

This was a single-center, cross-sectional study conducted in accordance with the Declaration of Helsinki principles after obtaining ethical consent from the local ethics committee with the number 80576354-050-99/280. The study was conducted with patients aged 65-90 years, who presented to Kafkas University Faculty of Medicine Ophthalmology Clinic between December 2019 and May 2020. All subjects included in the study were informed about the study. The best-corrected visual acuity (BCVA) of all patients included in the study was evaluated (Log-MAR), detailed ophthalmological examinations including the anterior and posterior segments were performed, and previously administered intravitreal anti-VEGF injection treatments were recorded.

The patients were referred to the cardiology department for the evaluation of CHF. Ejection fractions (EFs) were evaluated with echocardiography (Vivid 7, M4S probe, GE Vingmed Ultrasound AS, Horten Norway) by the same cardiologist (İ.R.). Patients with an EF below 40% were considered to have CHF. It was also inquired whether the patients were using any antihypertensive, and those using this drug were considered to have HT. For the remaining patients, blood pressure arterial values were measured after half an hour rest, and those with values over 140/80 were considered to have HT. Diabetic patients were also determined based on the presence of antidiabetic therapy (insulin or oral), a fasting glucose of 126 and above, or any given glucose level above 200.

A history of thromboembolic diseases, such as a previous stroke, myocardial infarction, and peripheral arterial disease was questioned, and if any of these diseases was present in epicrises in the patient information system, their scores were added to the scoring system.

Inclusion criteria: Patients between the ages of 65-90 years who stopped anti-VEGF treatment for at least three months due to AMD.

Exclusion criteria: Patients undergoing laser photocoagulation or intravitreal steroid injection, those with wet-type AMD due to high myopia, those with a history of pan or posterior uveitis.

Statistical analysis

Statistical evaluations were made using Statistical Package for the Social Sciences v. 21.0 (SPSS, Windows version Chicago, USA), and power analysis was undertaken using ClinCalc software (Rosner B. Fundamentals of Biostatistics. 7th ed. Boston, MA: Brooks/Cole; 2011. http://clincalc.com/stats/samplesize.aspx). Type I error (alpha value) 0.05 and power 80% of the study were calculated. While evaluating the study data, descriptive statistics, including the mean, standard deviation, median, frequency, ratio, minimum and maximum values were used. One-way analysis of variance test was used to analyze quantitative independent data. Subgroup analyses were evaluated by the post-hoc method. The chi-square test was used in the analysis of qualitative independent data. The receiver operating characteristic (ROC) curve analysis was performed to determine whether the CHADS2 or CHA2DS2-VASc score provided superior results. Statistical significance was accepted as $p < 0.05$.

RESULTS

A total of 295 patients were included in the study: 115 with wet-type AMD, 90 with dry-type AMD, and 90 controls without any retinal disease. There was no significant difference between the groups in terms of age and gender ($p = 0.078$ and 0.179, respectively). There was a significant difference in terms of BCVA ($p < 0.001$), while no significant difference was observed in EF ($p = 0.310$).

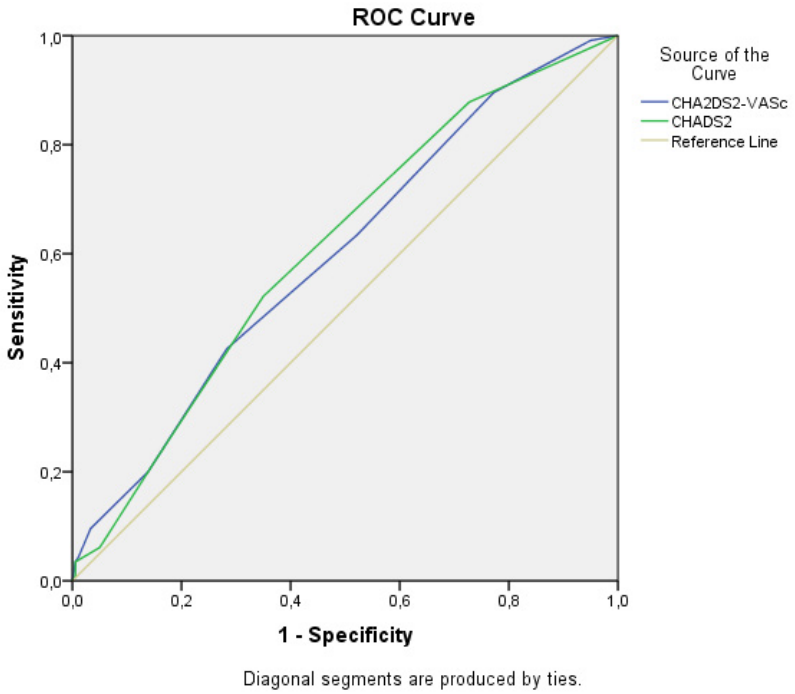
While there was no significant difference between the groups in terms of CHF, HT, and cerebrovascular disease (SVO), there was a significant difference in terms of DM and VD ($p = 0.246$, 0.215, 0.275, 0.032, and 0.011, respectively). There was also a significant difference between the groups in terms of the CHADS2 and CHA2DS2-VASc scores (Table 1). When the CHADS2 and CHA2DS2-VASc scores were compared using the ROC-curve analysis, the area under the curve values were 0.610 and 0.598, respectively. Neither scoring system had superiority over the other ($p > 0.05$) (Figure 1).

When the wet-type AMD patients were compared according to the treatment status, there was no significant difference in terms of age, gender, BCVA, and EF ($p =$

Table 1: *Demographic characteristics and CHADS2 - CHA2DS2-VASc scores of the patients according to groups*

Variable	Wet-AMD (n=115)	Dry-AMD (n=90)	Control (n=90)	p
Age (year)	73.8±9.2	74.2±9.6	71.2±9.7	0.078
Gender M/F(%)	48/67 (41.7/58.3)	48/42 (53.3/46.7)	47/43 (52.2/47.8)	0.179
BCVA (LogMAR)	0.853±0.920	0.356±0.619	0.119±0.853	<0.001
CHF (%)	27 (23.5)	16 (%17.8)	13 (14.4)	0.246
HT (%)	57 (43.2)	34 (25.8)	41 (31.1)	0.215
DM (%)	42 (36.8)	26 (28.9)	18 (20)	0.032
Stroke (%)	6 (5.3)	4 (4.4)	1 (1.1)	0.275
VD (%)	45 (39.5)	14 (15.6)	9 (10)	0.011
EF	52.6±10.1	55.1±9.1	55.8±8.5	0.310
CHADS2	1.72±1.18	1.48±1.29	1.10±0.97	0.01
CHADSVASC	3.32±1.66	2.91±1.61	2.52±1.42	0.02

One-Way ANOVA
AMD: age related macular degeneration, CHF: congestive heart failure, HT: hypertension, DM: diabetes mellitus, VD: Vascular disease, EF: ejection fraction.



Test Result Variable (s)	Area	Sensitivite	Spesifite	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
CHA2DVaS2	,598	0,635	0,478	,004	,533	,664
CHADS2	,610	0,522	0,650	,001	,545	,675

Figure 1: *Receiver operating characteristic (ROC) curve of CHADS2 ve CHA2DS2-VASc score in age-related macular degeneration. Although the area under curve (AUC) for the CHADS2 is higher compared to CHA2DS2-VASc but the difference was not significant alone (p > 0.05).*

0.244, 0.625, 0.102, and 0.389, respectively). While HT did not significantly differ, there was a significant difference in terms of DM, SVO and VD (p = 0.01, 0.02, and 0.01, respectively). When the groups classified according to the number of injections were compared in terms of the CHADS2 and CHA2DS2-VASc scores, it was observed that they both increased as the number of intravitreal injections (IVI) required for treatment increased, and there was a statistically significant difference between the groups (p = 0.01 and 0.05, respectively) (Table 2).

Table 2: *Demographic characteristics and CHADS2 - CHA2DS2-VASc scores of patients according to the number of intravitreal injections*

Variable	1-3 IVI (n=44)	4-8 IVI (n=43)	9 and above IVI (n=28)	p
Age (year)	75.3±9.14	73.7±9.7	71.5±8.3	0.244
Gender M/F (%)	16/28 (36.4/63.6)	20/23 (46.5/53.5)	12/16 (42.9/57.1)	0.625
BCVA (LogMAR)	0.769±0.886	0.886±0.920	0.958±1.04	0.102
EF	51.4±9.5	52.3±10.4	54.8±10.5	0.389
CHADS	1.34±0.80	1.70±0.98	2.36±1.66	0.01
CHADSVASC	2.80±1.17	3.37±1.49	4.07±2.22	0.05
CHF (%)	3 (6.8)	12 (27.9)	12 (42.9)	0.001
HT (%)	20 (46.5)	23 (53.5)	14 (50)	0.811
DM (%)	7 (16.3)	18 (41.9)	17 (60.7)	0.01
Stroke (%)	1 (2.3)	0 (0)	5 (17.9)	0.02
VD (%)	7 (16.3)	21 (48.8)	17 (60.7)	0.01

One-Way ANOVA
IVI: Intravitreal injection, EF: ejection fraction, CHF: congestive heart failure, HT: hypertension, DM: diabetes mellitus, VD: Vascular disease.

DISCUSSION

CHADS2 and CHA2DS2-VASc scores developed by cardiologists are designed to determine whether individuals are at risk for certain diseases, such as atrial fibrillation by taking into consideration age and systemic diseases. However, these systems were also later used in studies to estimate the prognosis of various diseases.[10-12] In these scoring systems, the diseases that pose risk for AMD such as age, DM, and HT are evaluated, and these scores can also be useful in predicting AMD or its treatment prognosis. In this study, it was found that the CHADS2 and CHA2DS2-VASc clinical scores were significantly higher in both dry and wet AMD patients compared to the control group. In the ROC analysis, both scores were determined to have the capacity to predict dry and wet AMD. In addition, when the wet AMD cases were evaluated in terms of the two scores, it was observed that those with high scores had higher need for injections.

The prevalence of dry-type and wet-type AMD increases exponentially with age. For this reason, older age is considered as the most important factor in AMD development. According to the results of a meta-analysis, female gender poses a higher risk for the development of wet AMD.[13] It was stated that this gender difference in the pathophysiology of macular degeneration may be due to hormonal changes, and the risk of macular degeneration is higher in the postmenopausal period.[14] In our study, although there was no difference between the dry AMD and control groups, the rate of women in the wet AMD group was significantly higher than those in the control group.

The prevalence of hypertension and AMD increases with age.[15] It has been suggested that localized arteriosclerosis, which resists the passage of nutrients from choriocapillaris to the retina, is effective in the pathophysiology of AMD. Although there are many studies showing a relationship between HT and AMD, there are also those reporting no relationship between the two diseases.[16-18] In our study, we found no significant relationship between HT and AMD and injection needs. This can be explained by the contradictory results of the relationship between HT and AMD, different racial and nutritional types of patients, HT duration, and patient compliance with treatment. Considering cardiovascular complications, we think it would be more useful to explain the relationship between HT and AMD. The CHADS2 and CHA2DS2-VASc scores used in our study may be more reliable in the evaluation of AMD, since they contain both HT and cardiovascular complications.

It has been suggested that DM may be a risk factor in the development of AMD, since it causes damage to the choroid, Bruch's membrane, and retinal pigment epithelium.[19] However, as in hypertension, there are studies revealing the relationship between DM and AMD, as well as those showing no relationship between them.[16,20] In our study, there was a significant relationship between DM and AMD, and the injection needs of patients with DM were also significantly higher than those without this comorbidity. These differences in the result may be due to previous studies excluding microvascular complication rates that show the effect of diabetes on tissues from their assessment. Clinical scoring used in our study may provide

clinically more reliable information since they evaluate DM and vascular complications together.

It has been determined that heart attack, heart failure, and hyperlipidemia pose a risk for AMD. In addition, HDL cholesterol levels are reported to be associated with AMD. It has been suggested that serum cholesterol poses a risk for the development of AMD by increasing atherosclerosis in choroidal vessels.[20-23] Since there is a relationship between coronary stenosis and early AMD, screening of patients with coronary artery disease in terms of AMD is recommended.[24] In a previous study, Klein et al. determined a relationship between advanced-stage AMD and carotid intima-media thickness and presence of plaque in carotid arteries. As a result, they suggested that the risk of AMD was increased since the nutrition of the outer retina was impaired.[25] In our study, there was a relationship between vascular disease prevalence and AMD. We also observed that those with a history of VD required a higher number of injections.

The limitations of our study include the unstandardized nature of intravitreal injection treatments and the scoring systems not including the evaluation of family history or body mass index. Another limitation can be considered as the absence of evaluating the severity of AMD before starting treatment. Therefore, there is a need for prospective large-series studies to determine the capacity of the CHADS2 and CHA2DS2-VASc clinical scores to predict AMD treatment.

CONCLUSION

CHADS2 and CHA2DS2-VASc clinical scoring systems can be predictors of AMD. They can also indicate the number of injections needed for treatment in clinical practice.

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