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C-reactive Protein Levels in Prediction of the Development or the Progression of Age-related Macular Degeneration in Patients Examined at Tuzla Canton

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ABSTRACT

Background: Age-related macular degeneration (ARMD) is a chronic, incurable, progressive, multifactorial, neurodegenerative disease, which is one of the leading causes of visual impairment, among individuals above 60 years of age in developed countries. Over the past decades, the role of inflammation and CRP in the pathogenesis of ARMD has been investigated. **Objective:** The study aimed to investigate the association between inflammation or CRP levels in prediction the development or the progression of ARMD. **Methods:** This retrospective-prospective, case-control study, was conducted at the Clinic for Eye Diseases, University Clinical Center Tuzla, from 2020. to 2024. Two group of participants were included in this study. The first group (n=100 patients) consisted of patients diagnosed with different stages of ARMD, and second, control group (n=100 patients) consisted of patients without ARMD. The study included subjects of both sexes, divided into three age categories (≤55; 56-66; ≥67 years). Detailed ocular and systemic evaluations were performed, including fundus examination and OCT angiography. A 5mL sample of venous blood was colected to determine serum CRP levels, for the both group of patients, using latex immunoassay method. Statistical analysis, including Student's t-test, Chi square test and posthoc (Turkey) tests, was conducted using SPSS 26 for Windows, with p<0,05 considered significant. **Results:** Out of 100 patients, 34 were having early, 18 intermediate and 48 were having advanced stages of ARMD. The mean serum CRP levels in the ARMD group (8.39±27.22mg/L) were significantly higher compared to the control group, (2.52±5.35mg/L), p=0,000. Also, serum CRP values by age category, between ARMD subjects and the control group, showed statistically significant differences in all age groups: ≤55 p=0.032; 56-66 p=0.019; ≥67 p=0.000. The mean serum CRP levels was 6.6±6.9 mg/L, 10±13.3 mg/L and 16±22.7 mg/L, in early, intermediate and advanced ARMD, respectively. Comparing these CRP values and different stages of ARMD, there were found statistically significant differences between the three stages. Furthermore, these results showed that mean CRP values increase with disease severity. **Conclusion:** Based on the obtained results serum CRP levels are significant risk factor in predicting the development and the progression of ARMD. Also, these results emphasize the role of systemic inflammation in the development and progression of ARMD.

Key words: age-related macular degeneration, inflammation, C-reactive protein

1. BACKGROUND

Age-related macular degeneration (ARMD) is a chronic, incurable, progressive, multifactorial, neurodegenerative disease (1). It is one of the leading causes of visual impairment in developed countries particulary among individuals above 60 years of age (2-4). The pathogenesis of this disease involves a large number of environmental and genetic factors, the development of chronic inflammatory reactions mediated by complement and the immune system, as well as angiogenesis (5, 6).

Numerous studies have evaluated the impact of various risk factors on the onset and progression of ARMD, but several studies have investigated the

relationship between serum CRP levels and the onset or the progression of ARMD.

The results of these studies are inconsistent and conflicting. An initial study on the correlation between increased CRP levels and ARMD progression was conducted by Seddon et al. (7) In this study, patients were divided into three groups, depending on the serum levels of CRP, so the first group included patients with a CRP level <0.5, the second 0.5-10 and the third >10mg/L. The results of this study showed that serum CRP values increase during disease progression. In the same study, after adjusting these results for age, sex, smoking, BMI, a statistically significant association of CRP with intermediate and advanced ARMD stages was found (OR for the highest and lowest quartile was 1.65 95%CI, 1.07-2.55 p=0.02). The authors of this study concluded that elevated CRP values represent an independent risk factor for ARMD, which may indicate the role of inflammation in the pathogenesis of this disease (7). This is supported by several studies, which also confirmed a positive association between elevated CRP levels and an increased risk of the onset and progression of ARMD (7, 8, 9, 10, 11). A recent studies using Mendelian randomization (MR) showed a positive correlation between serum CRP and ARMD, and strong genetic evidence that higher CRP levels increase the risk for all forms of ARMD (12, 13). However, some studies have not found a correlation between increased serum CRP levels and increased probability of ARMD (14, 15).

Over the past decades, authors have investigated the role of inflammation and CRP in the pathogenesis of ARMD. Recently, inflammation has been considered a key factor in the onset and progression of ARMD (7, 13, 15). Because of this, the author's research interest has increased in proving whether the level of CRP and other markers of inflammation is predictive in ARMD.

2. OBJECTIVE

The study aimed to investigate serum levels CRP (inflammation) in predicting the development or the progression of ARMD.

3. PATIENTS AND METHODS

Two group of participants were included in this study. The first group (n=100 patients) consisted of patients diagnosed with different forms and stages of ARMD, and second, control group (n=100 patients) consisted of patients without ARMD. The study included subjects (ARMD patients and control group) of both sexes, divided into three age categories (≤55; 56-66; ≥67 years). The patients data from retrospective part of the study were taken from the electronic hospital register. In the prospective part of the study were included outpatients suspected of having ARMD by indirect ophthalmoscopy. The inclusion criteria was the confirmation of the diagnosis of ARMD, regardless of the disease stage (early, intermediate or late). All patients with the presence of any other macular disease (e.g. epiretinal membrane, macular edema, etc.) or the presence of any other ocular disease (glaucoma, neuroopticopathy, etc.) or autoimmune inflammation disease were excluded from the study.

All participants in this study, underwent detailed systemic and ocular examination including: determination of visual acuity using the Snellen chart, testing of color vision using the Ishihara charts, examination of the posterior segment of the eye using a non-contact 90 D Volk lens, and scanning of the fundus with optical coherence tomography angiography (OCT-A) performed on the AngioVue system (RTVue XR Avanti, Optovue, Fremont, CA, USA). Serum CRP values were determined using Alinity c Vario reagent kit, latex immunoassay method on the Alinity c Abbott analyzer. Normal CRP values ≤ 5.0 mg/L. Of the total number of subjects (n=200), serum CRP values were determined in 97 ARMD cases and 91 in the control group.

Study design

This retrospective-prospective, case-control study, was conducted at the Clinic for Eye Diseases, University Clinical Center Tuzla, Bosnia and Herzegovina, from June 2020 to September 2024.

Ethical clearence

All patients who met the criteria for inclusion in this study, prior to their involvement, provided written informed consent, approved by Regional Comittee on Medical Ethics at University Clinical Centre Tuzla.

Statistical analysis

The data collected in the research were processed using standard statistical methods. In all statistical tests, a significance level of 5% was considered statistically significant. The comparison of the variables of the ARMD subjects with the control group was tested by Student's t-test. When testing the research objectives, a simple analysis of variance, Chi-square test and correlation of the connection of variable and non-variable variables, hierarchical regression analysis was used, based on which the contribution of classification, stage of ARMD was determined. Basic statistical parameters, measures of central tendency (the arithmetic mean, median and mode), measures of dispersion (standard deviation, error, minimum and maximum results), frequencies and percentages were calculated. Statistical processing was performed in the statistical program SPSS 26 for Windows.

4. RESULTS

In this study, which included 200 participants, divided into 100 ARMD cases and 100 control cases, the ARMD cases were significantly older compared to the control group in terms of average age (p=0.010) as well as in all age categories (p=0.016). No statistically significant difference was found in the gender distribution between these two groups of participants (p=0.076). The ARMD cases had sinificantly elevated mean serum CRP levels than control group (8.39±27.22mg/L vs. 2.52±5.35mg/L, p=0,002) ((Table 1).

A greater number of ARMD subjects (51 or 51%) were diagnosed with the wet form while the dry form was present in 49 (49%) patients (p=0.548). Considering the presentation (localization) of the disease, bilateral dis-

Variables	ARMD cases (n=100)	Control group (n=100)	p
Age (mean±SD)	73.03±69.39	65.76±69.39	0.010
Age group (mean±SD)			
≤55 years	53.50±49.90	46.30±49.90	
56-66 years	63.95±62.79	61.63±62.79	0.076
≥ 67 years	73.80±73.60	73.60±73.60	
Sex			
Male	74.43±69.85	65.27±69.85	0.016
Female	71.39±68.76	66.14±68.76	
CRP (mg/L) (mean±SD)	8.39±27.22 mg/L	2.52±5.35 mg/L	0.002

Table 1. Demographic comparison of ARMD cases and control group

Variable	F	M	N	
Forms ARMD	Wet	19	32	51
	Dry	27	22	49
Localization ARMD	UR	2	7	9
	UL	8	2	10
	Bilateral	36	45	81
Stages ARMD	Early	23	11	34
	Intermediate	10	8	18
	Advnced	13	35	48

Table 2. Forms, localization (unilateral or bilateral) and stages of ARMD. UR-unilateral right eye; UL-unilateral left eye

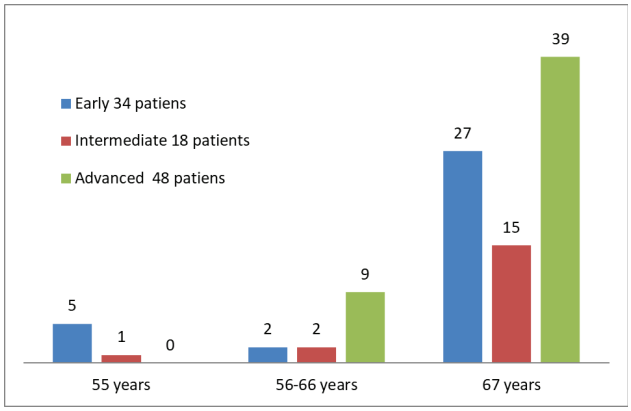

Figure 1. Different stages of ARMD in age categories

ease was the most common, observed in 81% of participants (36 women and 45 men). Of the total number of ARMD participants, 34 were in the early stage, 18 in the intermediate stage, and the largest number of patients, namely 48 (13 women and 35 men) in the advanced stage of the disease. (Table 2).

Analyzing the presence of different stages of ARMD in age categories, it was found that all three stages are most often present in the age group of ≥67 years (early 27 patients; intermediate 15 and advanced 39 patients) (Figure 1).

Furthermore, comparing mean CRP levels in the different stages of ARMD (early, intermediate, advanced), statistically significant differences were found for all stages of ARMD (p=0.031). The highest values were found in advanced stages of the disease. The serum CRP levels increase as the disease progresses in all age categories (Table 3).

	Early	Intermediate	Advanced	p
≤55 years	2.5±2.7	2.8±1.9	4.0±4.9	0.032
56-66 years	3.4±3.9	3.9±2.5	5.4±6.3	0.019
≥ 67 years	15.3±17.4	24-1±24.4	38.6±48.0	0.000
CRP (mg/L) (mean±SD)	6.4±6.9 mg/L	10.0±13.3mg/L	16.0±22.7 mg/L	0.031

Table 3.Association mean CRP levels in age group with different stage of ARMD

5. DISCUSSION

In our study, we investigated the link between inflammation with CRP, a systemic marker of inflammation, in predicting the onset and progression of ARMD. A total number of 200 participants were divided into ARMD patients and control group (non ARMD patients). The mean age of ARMD patients was 73.03±9.02 years compared to 65.76±10.33 years in controls, with a significant age difference (p=0.010). Also, ARMD participants were significantly older compared to the control group in age categories (p=0.016). In the study by Čolak et al. (16) the mean age of the ARMD patients was 71.47±7.02 which was quite similar to our study, probably because of large number of patients in advanced ARMD stages as well as in our study. The results of our study confirm the universal conclusion that ARMD occurs in older age, and age is the only constant and unchangeable risk factor for the development and progression of ARMD (17, 18). The results of other studies, as well as ours, did not confirm a significant association between gender distribution and ARMD (19, 20, 21, 22).

In our study, 51 patients were diagnosed with the wet form of ARMD, while the dry form was present in 49 subjects (p=0.548). Similar results were obtained in the study by Čolak et al. (16) where the wet form (advanced exudative form) is found in 58 subjects, and 40 of them had unilateral while 18 had bilateral presentation of the disease. Bilateral presentation of ARMD, in our study had 81 subjects, while unilateral presentation was found in 19 patients. The almost equal representation of dry and wet forms of ARMD, in our study, is probably a consequence of a slightly larger number of male (54%) than female (46%), possibly because men more often had bad lifestyle habits, including smoking, alcohol consumption, diet, etc. Other reasons for such results could be irregular check-up patients by an ophthalmologist or some specifics in the organization of healthcare.

Some authors believe that ARMD patients first develop the dry form, and the wet develops on the background of the dry form, so the dry form can be considered a precursor to the wet form (23, 24). Friedman et al. report that approximately 20% of patients with dry ARMD progress to the wet form (25). A confirmation of these assertions are the results of the presence of bilateral ARMD presentation, in the largest number of subjects (81 cases) in our study.

Early stage was found in 34 subjects, and it is most common in the age categories <55 years while intermediate was found in 18 subjects, and it is most common in the 56-61 age categories. The largest number of subjects

(48 subjects) had an advanced stage of the disease and belonged to the age category ≥67 years (mean age 73,80 years). Similar results were found in study Borooah et al. (22). In the same study (22), advanced ARMD (in 21.42% patients) was predominantly observed in patients over 71 years, highlighting age as a critical risk factor for disease progression (p<0,05). Other supporting studies confirm that ARMD prevalence increases with age with older individuals at higher risk of advanced stages (3, 18).

Recently, it is considered that inflammation is one of the key risk factors in ARMD (7, 13, 15) and the author's research interest has increased in proving whether the level of CRP is predictive of the onset or progression of ARMD. In some studies, the association between CRP levels and ARMD has been proven, while in others this association has not been confirmed. The results of research, the association between CRP levels and ARMD are quite inconsistent. Kurtul et al. (26) demonstrated, in their study, significant association between elevated highly sensitive CRP and neovascular ARMD. In the Rotterdam study, de Jong et al. (27) showed a small significant association between log CRP levels and ARMD incident. The Rotterdam study (28), in the large population-based cohort, found that elevated baseline levels of highly sensitive CRP were associated with development of early and late stages of ARMD. Kikuchi et al. (29) demonstrated the trends of the increased risk of disease with increase in CRP levels, which were statistically significant for both neovascular ARMD and polypoidal choroidal vasculopathy. However, in the study by Boey et al. (30), no association was found between CRP and ARMD or cataract, in the general population of the Asian people, while higher CRP was associated with ARMD in individuals without diabetes.

The results obtained in our study, showed that mean serum CRP levels were significantly higher (p=0,000) in ARMD subjects (8.39±27.22mg/L) compared to the control group (2.52± 5.35mg/L), These obtained results highlight the strong link between CRP (inflammation) in predicting the development of disease.

Furthermore, comparing CRP levels in the stages of ARMD (early, intermediate, advanced), statistically significant differences were found for all stages of ARMD (p=0,031). CRP showed a significant increase with progression of ARMD with the highest values observed in advanced stages (16.0±27.22mg/L). The mean CRP values were lowest in the early (6,4±6,9 mg/L) stage of the disease while mean values in intermediate stages were 10.0±13.3 mg/L. These obtained results highlight the strong link between CRP or inflammation in predicting the progression of disease.

6. CONCLUSION

The existence of statistically significant differences in mean serum CRP values between ARMD subjects and the control group make this marker a significant risk factor in predicting the development of ARMD. Also, elevated CRP levels in different stages of ARMD makes this marker a significant risk factor in predicting the progression of ARMD. These obtained results emphasize the role of systemic inflammation in the development and progression of ARMD.

The results of this study highlight the need for prospective longitudinal population studies based on a more precise assessment and classification of participants according to disease phenotype. These studies should include continuous clinical monitoring and multiple measurements of inflammatory markers from various biological samples.

This is the first study in Tuzla Canton that uses this approach in researching the connection between inflammation with CRP as marker of systemic inflammation in predicting the development and the progression of ARMD.

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