Complete blood cell count-derived inflammation biomarkers in men with age-related macular degeneration

Complete blood cell count-derived inflammation biomarkers in men with Age-Related Macular Degeneration

Abbreviated title: CBC-derived inflammation biomarkers in AMD

Antonio Pinna, MD,[1,3] Tiziana Porcu, MD,[1] Giuseppe D'Amico-Ricci, MD,[2] Stefano Dore, MD,[1,3] Francesco Boscia, MD,[1,3] Panagiotis Paliogiannis, PhD,[2] Ciriaco Carru, PhD,[2,3] Angelo Zinellu, PhD,[2]

[1]Department of Medical, Surgical, and Experimental Sciences, University of Sassari, Sassari, Italy

[2]Department of Biomedical Sciences, University of Sassari, Sassari, Italy.

[3]Azienda Ospedaliero-Universitaria di Sassari, Sassari, Italy

Corresponding Author: Antonio Pinna, MD, Department of Medical, Surgical, and Experimental Sciences, Ophthalmology Unit, University of Sassari, Viale San Pietro 43 A, 07100 Sassari, Italy. E-mail: apinna@uniss.it.

Purpose: To investigate the role of some blood count-derived inflammation biomarkers in age-related macular degeneration (AMD).

Methods: 79 men with late-stage AMD and 79 male, age-matched cataract controls without AMD were recruited in March-December 2016. A blood sample was taken. The following blood cell count-derived indexes were evaluated: neutrophil/lymphocyte ratio (NLR), derived NLR [dNLR=neutrophils/(white blood cells–neutrophils)], platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), (neutrophils*monocytes)/lymphocyte ratio (SIRI), and (neutrophils*monocytes*platelets)/lymphocyte ratio (AISI).

Results: AMD patients had significantly lower median values of white blood cells, monocytes, neutrophils, platelets and mean platelet volume (MPV). Regarding the combined indexes, only AISI was significantly lower in AMD patients than in controls. Receiver operating characteristics curve analysis revealed that the ability of AISI and MPV to predict AMD is poor.

Conclusion: Results suggests that NLR, dNLR, PLR, MLR, SIRI and AISI are unreliable disease biomarkers in men with AMD. Larger scale studies are necessary to confirm these findings.

Introduction

Age-related macular degeneration (AMD) is a leading cause of central vision loss in adults aged over 50 in the Western Countries.[1] AMD can be divided into two forms: early and late. Early AMD is a clinical condition without clearly evident visual symptoms, showing drusen and/or retinal pigment epithelium alterations in the macula.[2] The late-stage manifestations of AMD include geographic atrophy (dry AMD) and neovascolar (wet) AMD. The pathological mechanisms underlying AMD are not clear, but genetic predisposition and environmental factors, including tobacco smoking and oxidative stress, are thought to play a key role.[3-9]

Similarly to other chronic, progressive disorders related to ageing (e.g., atherosclerosis and Alzheimer's disease), inflammation contributes to the pathogenesis of AMD. The role of inflammation is supported by the detection of immune system products in the drusen and by the findings of genome-wide association studies, which have implicated several components of the complement cascade in AMD pathogenesis.[10-12]

Inflammation results from a complex network of interactions involving immune-related cells, such as neutrophils, lymphocytes, and macrophages. Clinical evidence indicates that the absolute counts of white blood cells (WBC), neutrophils, and lymphocytes, and their ratios, can adequately reflect chronic inflammatory conditions.[13] The neutrophil/lymphocyte ratio (NLR) has been increasingly put forward as a marker of systemic inflammation. NLR may be an independent prognostic factor in several solid tumors and has been associated with some chronic diseases with inflammatory features.[14] Furthermore, recent reports have shown an elevated NLR in AMD patients.[15-17]

The present study was undertaken to investigate the role of NLR and other complete blood cell count (CBC)-derived inflammation biomarkers in AMD.

Methods

The present study used a case-control design, recruiting 79 consecutive men with late-stage AMD and 79 perfectly age-matched male controls without AMD between March and December 2016. Only men were enrolled, because this investigation was part of a larger study designed to assess the role of Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency in AMD. In this X-linked recessive disease, only hemizygous males have a total enzyme deficiency.

Institutional ethics review board approval was obtained and the study was conducted in full accord with the tenets of the Declaration of Helsinki. Each participant received detailed information and provided informed consent before inclusion.

The inclusion criteria for cases were male gender, Sardinian descent, and the diagnosis of late-stage AMD (neovascular AMD or geographic atrophy involving the center of the macula)[2] in at least one eye. All AMD patients underwent a full ophthalmic evaluation, including fluorescein angiography and OCT scans of the macula (3D OCT-1000 Mark II, Topcon Co, Tokyo, Japan).

Perfectly age-matched male controls of Sardinian ancestry were selected among patients undergoing cataract surgery. All controls underwent standard ophthalmic evaluation, including best corrected visual acuity (BCVA), slit-lamp examination, applanation tonometry, and fundus examination. Patients with any clinical evidence of maculopathy and/or retinal vascular disorder were excluded.

Medical conditions, including body mass index (BMI), systemic hypertension, diabetes mellitus, and renal failure were also recorded for both AMD patients and controls. Definitions of systemic hypertension and diabetes mellitus have been reported previously.[18]

Smoking history was obtained by an interviewer-administered questionnaire. Current smoking status was compared with noncurrent smoking (individuals who smoked in the past or never smoked).

Blood samples were collected and blood cell counts were performed using an automatic blood counter Cell-Dyn Sapphire (Abbott Diagnostics, Santa Clara, CA, USA).

The following combined indexes were evaluated: NLR, derived NLR [dNLR = neutrophils/(white blood cells - neutrophils)], platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), (neutrophils x monocytes)/lymphocyte ratio (SIRI), and (neutrophils x monocytes x platelets)/lymphocyte ratio (AISI).

All results are reported as mean or median values, as appropriate. Variables distribution was assessed by Shapiro-Wilk test. Statistical differences between groups were evaluated using unpaired Student's t-test, Welch-test for data with unequal variances, or Mann-Whitney rank sum test, as appropriate. The ability of AISI and mean platelet volume (MPV) to predict AMD was analyzed using receiver operating characteristics (ROC) curve analysis. Optimal cut-off maximizing sensitivity and specificity was selected. Sensitivity and specificity were reported using the optimal ROC curve value according to Youden Index. Statistical analysis was performed using MedCalc for Windows, version 15.4 64 bit (MedCalc Software, Ostend, Belgium).

Results

The study group consisted of 79 AMD men (mean age: 78±7 years, range 57-92 years). The control group included an equal number of perfectly age-matched male subjects without AMD. In both groups, all individuals were of Sardinian ancestry.

In the AMD group, 19 patients had bilateral wet AMD, 1 bilateral geographic atrophy, 3 wet AMD in one eye and geographic atrophy in the fellow one, and 56 wet AMD in one eye and early AMD in the fellow eye.

Wet AMD patients had received an average of 5 intravitreal injections of an anti-VEGF agent (bevacizumab, ranibizumab, or aflibercept) per eye.

Demographics, medical history information, and CBC results are summarized in Table 1. All the diabetic patients had type 2 diabetes. Both AMD patients and control subjects had similar rates of diabetes, systemic hypertension, chronic renal failure, and smoking. Likewise, there were no significant differences in BMI, lymphocytes, and red cell distribution width (RDW) values. On the other hand, AMD patients had significantly lower median values of white blood cells (WBC), monocytes, neutrophils, platelets and MPV. Similar significant differences were also found when AMD patients were categorized into bilateral (56) or monolateral (23) forms (data not shown).

Results of combined indexes are shown in Table 2. Only AISI was found to be significantly lower in AMD patients than in cataract controls.

We performed ROC analysis for MPV and AISI, alone and in combination (Table 3). The best cut-off values were 7.7 and 0.22, respectively. In both cases, the area under the curve (AUC) results were relatively poor.

Discussion

NLR is a widely available, easy to determine, and inexpensive inflammation index, which has been extensively studied as a predictor of disease development, progression, and prognosis and response to medications. The rationale behind NLR involves disease-related modifications of the most representative cell populations responsible for inflammation. It is well established that NLR values increase in several malignancies and correlate well with cancer stage and survival.[14,19,20] NLR has also been shown to correlate with disease activity and outcome in several chronic inflammatory diseases, such as arthritis, systemic hypertension, diabetes mellitus, and chronic obstructive pulmonary disease;[14,21,22] in particular, a correlation between NLR and the severity of diabetic retinopathy has been demonstrated.[23] Similar observations have also been reported for other composite CBC-derived indexes, such as PLR, MLR, and SIRI.[21,22,24] Furthermore, modifications in CBC dimensional indexes, such as RDW and MPV, have been shown to reflect the intensity of inflammation in several diseases, as systemic inflammation not only hinders the survival of erythrocytes and platelets, but also deforms their membranes.[25,26]

Inflammation is thought to play an important role in the pathogenesis of AMD.[27] In the ageing retina, reactive oxygen species (ROS) are considered to be major causes of tissue stress and serve as local triggers for retinal para-inflammation. Furthermore, in AMD, microarray studies have shown the up-regulation of genes involved in complement activation and inflammatory cytokine/chemokine production, such as IL-6, TNF-α, MCP-1.[27]

Former investigations have assessed the role of NLR in AMD. Ilhan et al.[15] found higher NLR values and a correlation between NLR and disease severity in AMD patients. In another study, Kurtul and Ozer reported that increased NLR is independently associated with neovascular AMD, with sensitivity and specificity of 73% and 60%, respectively.[16] More recently, Sengul et al.[17] have observed that NLR and PLR levels are higher, inversely proportional to BCVA, and directly proportional to central macular thickness in neovascular AMD. These authors also found that ROC curves for NLR and PLR predicted neovascular AMD with a sensitivity and specificity of approximately 90%. Overall, these reports emphasize that NLR and PLR correlate with disease severity and may be useful biomarker of inflammation in AMD.[15-17] However, it is important to note that the above-mentioned studies made no gender distinction when results were analyzed, an approach that raises the crucial question of whether, or not, there still exist differences between AMD patients and controls after categorization by gender.

In our survey, we found that AMD patients had a significantly lower WBC count. Previous epidemiological investigations have shown conflicting results regarding the association between WBC count and AMD. Whereas multiple studies have reported correlations between higher WBC counts and an increased risk of AMD,[15,16,28-30] other studies have failed to find such an association.[31-33] This evidence is further complicated by our finding, showing an inverse correlation, i.e. that a higher WBC count is associated with a lower risk of AMD. Overall, these results suggest that the role of leukocyte count in AMD is far from clear.

Unlike the studies from Turkey,[15-17] we failed to find any statistically significant difference in NLR and PLR values between men with AMD and cataract controls without AMD. A similar result was obtained, when we assessed other combined indexes, such as dNLR, MLR, and SIRI. Only AISI was found to be significantly lower in AMD patients; however, ROC analysis disclosed that this result was associated with low sensibility (54%) and specificity (69%).

Our study has several important limitations. First, the sample size, though similar to that reported in other studies,[15-17] was relatively small. Second, it was restricted to a limited, genetically homogeneous group of patients (i.e. those of Sardinian descent). Therefore, our findings may not be applicable to AMD patients of non-Sardinian ancestry. Third, as this study was performed only on men, we have no idea of whether, or not, our results can be extended to women. Last, but not least, even though both neovascular and dry forms of AMD have common underlying pathological features and causes, we analyzed a small number of patients with geographic atrophy.

In conclusion, the role of WBC count and CBC-derived inflammation biomarkers in AMD is far from clear. Overall, our result support the idea that NLR, dNLR, PLR, MLR, SIRI and AISI are not reliable disease biomarkers in men with AMD. These findings need to be confirmed by larger scale studies, also involving patients of non-Sardinian ancestry.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Demographics, medical history information, and blood count results of male patients with age-related macular degeneration (AMD) and cataract controls without AMD.

	AMD patients (n = 79)	Controls (n = 79)	p-value (Cases vs Controls)
Age, years, mean ± SD	78±7	78±7	1
Body mass index (kg/cm^2), mean ± SD	27.2 ± 5.5	27.1 ±3.7	0.84
Smoking, n (%)	11 (8.7)	11 (8.7)	1
Chronic renal failure, n (%)	3 (3.8)	2 (2.5)	0.65
Systemic hypertension, n (%)*	55 (69.6)	51 (64.6)	0.5
Diabetes mellitus, n (%)†	14 (17.7)	20 (25.3)	0.25
G6PD‡ deficiency, n (%)	7 (8.9)	8 (10.1)	0.79
White blood cell count (x10^9/L), median (IQR)!	7.51 (6.76-8.90)	6.85 (5.67-7.90)	0.0035
Monocytes (x10^9/L), median (IQR)	0.5 (0.4-0.6)	0.5 (0.4-0.7)	0.038
Lymphocytes (x10^9/L), median (IQR)	1.7 (1.30-2.20)	1.8 (1.40-2.33)	0.35
Neutrophils (x10^9/L), median (IQR)	4.1 (3.53-5.00)	4.5 (3.98-5.55)	0.025
Platelet (x10^9/L), median (IQR)	194 (166-220)	210 (180-235)	0.055
Mean platelet volume (fl), median (IQR)	7.5 (6.9-8.1)	8.2 (7.4-8.9)	0.0007
Red cell distribution width (%), median (IQR)	14.2 (13.2-15.6)	14.0 (12.8-15.1)	0.17

* Blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic or taking antihypertensive medication.

† Fasting plasma glucose ≥126 mg/dL and/or plasma glucose ≥200 mg/dL 2 hours after a 75-g oral glucose load or taking insulin or oral hypoglycemics.

‡ G6PD: Glucose-6-Phosphate Dehydrogenase

! IQR: interquartile range.

Table 2. Complete blood cell count-derived indexes in men with age-related macular degeneration (AMD) and cataract controls without AMD.

	AMD patients (79) Median (IQR)*	Controls (79) Median (IQR)*	p-value (Cases vs Controls)
Neutrophil/lymphocyte ratio (NLR)	2.36 (1.70-3.17)	2.55 (1.85-3.12)	0.32
Derived neutrophil/lymphocyte ratio (dNLR)†	1.51 (0.56-1.99)	1.58 (1.22-2.05)	0.87
Platelet/lymphocyte ratio (PLR)	111 (83-148)	119 (90-146)	0.33
Monocyte/lymphocyte ratio (MLR)	0.29 (0.21-0.38)	0.29 (0.25-0.36)	0.47
SIRI‡	1.08 (0.74-1.78)	1.26 (0.98-2.01)	0.1
AISI§	205 (134-353)	294 (183-390)	0.018

*IQR: interquartile range

†dNLR: neutrophils / (white blood cells - neutrophils) ratio

‡SIRI: (neutrophils x monocytes)/ lymphocyte ratio

§AISI: (neutrophils x monocytes x platelets)/lymphocyte ratio

Table 3. Receiver operating characteristics (ROC) curves and prognostic accuracy of (neutrophils x monocytes x platelets)/lymphocyte ratio (AISI) and mean platelet volume (MPV), alone and in combination (AISI-MPV).

Marker	AUC	95%CI	p value	Cut-off	Sensibility	Specificity
AISI	0.61	0.53-0.69	0.016	<0.220	54%	69%
MPV	0.66	0.58-0.73	0.0004	<7.7	63%	68%
AISI-MPV	0.67	0.59-0.74	0.0002	>0.502	71%	66%