Assessment of Neutrophil-Lymphocyte Ratios in Patients with Dry Age-related Macular Degeneration

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Abstract

Purpose: To assess the significance of neutrophil-lymphocyte ratio (NLR) as an inflammatory indicator in patients with dry age-related macular degeneration (AMD).

Study design: A retrospective case-control study.

Methods: Clinical diagnosis along with complete blood count (CBC) results were extracted from hospital and laboratory information systems for patients with dry-AMD and age/gender-matched controls attending the ophthalmology clinic at King Abdulaziz medical city, Jeddah, Saudi Arabia, between 2018-2020. NLR was calculated by dividing the neutrophil by the lymphocyte count.

Results: This study captured 90 patients diagnosed with dry-AMD and 270 control subjects without AMD. The mean of ages 70 and 71 years old for cases and controls, respectively. In univariate analysis, there were no significant differences in CBC results between cases and control. In NLR, dry-AMD patients have a slightly higher mean than the control group; however, this increase was not statistically significant (P -value 0.8). In the NLR model, age and gender were statistically significant factors affecting the NLR values in dry-AMD (P -value 0.03, 0.01 respectively).

Conclusion: as a systemic inflammatory biomarker, NLR alone could not predict dry-AMD. However, the slight increase in the NLR values may be helpful if augmented with other laboratory measurements to aid in early disease prediction.

Background

Age-related macular degeneration (AMD) is the third leading cause of blindness following cataracts and glaucoma (Abner et al., 2002). Yet, it is the leading cause of blindness in patients over 50 years of age (Al-Ghamdi, 2019; Hajar et al., 2015) and the fourth leading cause of low vision in the Saudi population (Z Alotaibi, 2015). AMD is caused by the accumulation of drusen in the macula with or without geographic atrophy, resulting in different levels of visual impairment and/or blindness. AMD starts dry (non-neovascular or non-exudative) and can progress into the wet form (neovascular or exudative) with or without retinal pigment detachment in the macular region. Wet AMD is responsible for the majority of severe vision loss (Wong et al., 2014).

According to the Saudi General Authority for Statistics (2018 report), over 90% of the Saudi population is under 50 years of age. With the aging population, the number of AMD patients is expected to increase, which would lead to heavy health, social, and economic burden (Pascolini & Mariotti, 2012; Wong et al., 2014). The Saudi elderly population (≥ 60) is projected to increase from 3% in 2010 to 9.5% and 18.4% in 2035 and 2050, respectively (Khoja et al., 2018). Because of the disease's silent onset, it is rational to investigate potential novel biomarkers to aid in early prediction, diagnosis, and prognosis of AMD. Early detection will ultimately allow proper utilization of the available AMD management options to prevent or slow vision loss. AMD pathogenesis is not yet fully understood. Our knowledge about AMD risk factors is

limited to a complex of factors such as genetic makeup, environmental stimuli, and metabolic features (Çolak et al., 2018; Velez-Montoya et al., 2014; Zarbin, 2004).

The role of NLR as a simple, reliable, and low-cost inflammatory biomarker in ocular conditions is yet unclear. Several reports have demonstrated a correlation between NLR and wet AMD (Reviewed in Niazi et al., 2019). However, the link between NLR and dry AMD is based on a limited number of studies (Ilhan et al., 2015; Kurtul & Ozer, 2016), limiting our insight into the starting phase of the disease. This study aims to assess the levels of NLR in patients with dry AMD.

Methods

Study population

Institutional review board and ethics committee approval was obtained from King Abdullah international medical research center (Study number SP21J/083/03). While maintaining participants' confidentiality and anonymity, electronic health records (January 2018 - December 2020) were collected for new patients with dry AMD, ≥ 50 years, with evidence of macular drusen in at least one eye, with or without signs of geographic atrophy, and complete blood count (CBC) laboratory results. NLR was calculated by dividing the neutrophil ($\times 10^9/L$) by the lymphocyte ($\times 10^9/L$) count. Similar data were collected for age- and sex-matched cataract group without AMD as a control. Electronic health records were compiled from King Abdulaziz medical city (Jeddah, Saudi Arabia), which provides primary, secondary, and tertiary care. The study was performed following the Declaration of Helsinki principles, and informed consent was obtained from all participants.

Sample size calculation

The survivor sampling technique was used with a control group consisting of individuals from the source population who do not have the outcome of interest (with no AMD). For sample size calculation, a matched case-control study was used (the case-control ratio is 1:3).

Statistical analysis

In univariate analysis, associations between demographics and blood results characteristics were assessed across cases and control groups using the chi-square for categorical data and t-test for numeric variables. Multivariate analyses adjusted for age and gender were conducted to examine the differences between cases and control groups. Models were assessed using analysis of covariance according to the nature of our outcome. We checked assumptions of the linear relationship between the dependent variable and the covariate and homogeneity of regression slopes, and all models met the assumptions. *P*-values were two-sided; all confidence intervals were at 95 %. All analyses were conducted using the SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC).

Results

From January 2018 to December 2020, this study captured 90 cases of patients diagnosed with dry AMD and 270 control subjects without AMD. The mean of ages 70 and 71 years old for cases and controls, respectively. CBC results are summarized in table 1.

In univariate analysis (Table 1), there were no significant differences in CBC results between cases and control groups. In Platelet results, control groups tend to have a slightly higher mean (268.73) than cases group mean 268.68 with a P -value of 0.0001. In terms of mean corpuscular hemoglobin, the cases group showed a lower mean of 27.9 than the control group, 28.27. In NLR, dry AMD patients have a slightly higher mean than the control group (2.46 and 1.98, respectively). However, this increase was not statistically significant (P -value 0.8). The same pattern was observed in mean corpuscular volume, where the case group showed a lower mean than the control group (86.54 and 86.64, respectively). Regression models adjusted for age and gender were summarized in tables 2-3, and figure 1. Age and gender were statistically significant factors affecting NLR values in cases compared to the control group (P -value 0.03, 0.01 respectively). No other CBC parameters showed any significant difference between cases and the control group.

Discussion

The NLR has been increasingly investigated as a systemic inflammation marker. Several studies have analyzed NLR in inflammatory conditions as an indicator of the disease, progression, and severity. For instance, positive NLR correlation was reported in diabetic retinopathy, worsening renal function in diabetic patients, end-stage renal disease, metabolic syndrome, ulcerative colitis, coronary artery disease, papillary microcarcinomas, pancreatitis, and cardiovascular diseases (Ulu et al., 2013; Azab et al., 2012; Turkmen et al., 2014; Buyukkaya et al., 2014; Okba et al., 2019; Torun et al., 2012; Papa et al., 2008; Seretis et al., 2013; Suppiah et al., 2013; Afari & Bhat, 2016; Cupp et al., 2020).

In AMD, Ilhan et al. (2015) has reported a significant difference in NLR values between dry and wet AMD ($p=0.017$), wet AMD and controls ($p<0.001$), and dry AMD and controls ($p<0.001$). Other reports have shown that elevated NLR was significantly correlated with wet AMD (Niazi et al., 2019). This study found that NLR values were slightly elevated in dry AMD patients compared to control; however, this was not statistically significant. The slight increase may correlate well with our newly diagnosed patient cohort.

Inflammatory mechanisms have been reported in the progressing of both dry and wet AMD (Xu et al., 2009). The accumulation of drusens between the retinal pigment epithelium and Bruch's membrane is a significant risk factor for the progression of AMD. These pathological drusens can trigger a cascade of chronic inflammatory and immune-mediated processes (Hageman et al., 2001; Rivera et al., 2017). Golestaneh et al. (2017) have shown that impairment in autophagic processes can contribute to drusens accumulation. In addition to the increased reactive oxygen species (ROS) and the reduced mitochondrial activity observed in retinal pigment epithelial cells cultured from human donors with AMD compared to healthy donors. With aging, mitochondria accumulate ROS damage and become dysfunctional, resulting in a notable decline in mitochondrial health, in addition to the decrease of autophagic processes (Picca et

al., 2017). The accumulation of oxidative damage is believed to be a leading cause of age-related degenerative diseases such as cancer, Alzheimer's disease, and AMD pathological processes (Chen & Xu, 2015; Datta et al., 2017; Golestaneh et al., 2017; Heppner et al., 2015; Matsui et al., 2000; Saijo et al., 2016).

Furthermore, the damaged mitochondria release components such as mitochondrial DNA (mtDNA), which induces inflammatory responses. A study by Lin et al., (2011) has shown that the increase in age-related mtDNA damage can lead to more macula lesions that positively correlate with AMD progression. Sensing mtDNA by cytosolic innate immune sensors, cyclic-GMP-AMP synthase, and the stimulator of interferon genes, lead to the production of Type I interferons (Type I IFNs) and other pro-inflammatory cytokines (Kumar, 2019). Additionally, mtDNA also triggers the assembly of a multiprotein complex known as the inflammasome (Shimada et al., 2012a). NOD-like receptors, and absent in melanoma 2-like receptors, are the two major sensors known to date responsible for the induction of inflammatory responses via the assembly of the inflammasome. Assembly of the inflammasomes leads to the production of inflammasome-mediated cytokines, IL-1 β and IL-18, and eventually the pyroptotic type of cell death (Elinav et al., 2011; Keating et al., 2011). In relevance, mounting evidence suggested that mitochondria play an important role in activating the NOD-like receptors family pyrin domain containing 3 (NLRP3) inflammasome. It has been demonstrated that mitochondrial damage and the cytosolic release of mitochondrial ROS and mtDNA increase NLRP3 activation (Shimada *et al.*, 2012; Zhou R. *et al.*, 2011). Therefore, inflammasome activation by mtDNA and the progression of AMD needs to be investigated. The role of the NLRP3 inflammasome in AMD pathogenesis has been shown using the amyloid-beta (A β) component of drusen as a stimulus which resulted in a robust inflammasome activation evident by elevated levels of IL-1 β and IL-18. In addition to inflammasome-mediated-cytokines, stimulation with A β resulted in upregulation of the pro-inflammatory cytokines, IL-6 and TNF- α (Liu et al., 2013). Therefore, further studies are essential to investigate the levels of inflammatory markers including type I IFNs, IL-1 β , IL-18, IL-6, and TNF- α in patients with dry and wet AMD compared to control participants.

Conclusion

As a routine laboratory test, it is important to note that NLR is not specific for either type of AMD and can be elevated in several diseases and malignancies. The disease is also often associated with other age-dependent comorbidities, which could influence NLR values. Therefore, further studies are essential to generate robust evidence to investigate causality and NLR values clinical utility in line with other inflammatory biomarkers.

Abbreviations

AMD
age-related macular degeneration
A β
amyloid-beta

CBC
complete blood count
IFNs
interferons
IL
Interleukins
mtDNA
mitochondrial DNA
NLR
Neutrophil-lymphocyte ratio
NLRP3
NOD-like receptors family pyrin domain containing 3
ROS
reactive oxygen species

Declarations

Ethics approval and consent to participate: IRB approval was obtained from King Abdulla international medical research center (#SP21J/083/03).

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Tables

Table.1 Baseline demographic and clinical characteristics of dry AMD cases and controls			
	dry AMD n (%) ¹	Controls n (%)	p-value cases vs. controls ²
Total	90 (22.55)	270 (77.44)	-
Age, years, mean $\pm$ SD	71 $\pm$ 9	70 $\pm$ 7	0.27
Gender			
Male	41 (45.56)	132 (42.72)	0.63
Female	49 (54.44)	177 (57.28)	
Hematological parameters	Means (upper,lower)		
Red blood cells (10 ¹² /l)	4.66 (4.55, 4.78)	4.56 (4.5, 4.62)	0.21
Hemoglobin (g/dl)	14.34 (11.92, 16.77)	13.25 (12.63, 13.87)	0.49
Mean Corpuscular Hemoglobin (pg)	27.9 (27.37, 28.42)	28.27 (27.97, 28.56)	0.9
Mean corpuscular volume (fL)	86.4 (84.5, 88.37)	85.8 (84.5, 86.1)	0.43
White blood cells (10 ⁹ /l)	7.71 (7.07, 8.34)	7.95 (7.47, 8.44)	0.21
Platelet (10 ⁹ /l)	268.61 (254.23, 283)	268.73 (260.168, 277.31)	<0.0001
Mean platelet volume (fL)	8.35 (8.12, 8.57)	8.28 (8.17, 8.39)	0.87
Red cell distribution width (%)	13.91 (13.57, 14.24)	14.31 (13.63, 14.98)	0.11
Mean corpuscular hemoglobin concentration (g/dl)	36.97 (30.27, 43.67)	34.36 (32.21, 36.52)	0.74
Eosinophils (10 ⁹ /l)	0.52 (0.28, 0.76)	1.61 (-0.65, 3.86)	0.62
Monocytes (10 ⁹ /l)	0.63 (0.57, 0.68)	0.602 (0.57, 0.62)	0.63
Neutrophils (10 ⁹ /l)	4.55 (3.75, 5.32)	4.2 (3.76, 5.63)	0.79
Lymphocytes (10 ⁹ /l)	2.29 (2.11, 2.47)	2.39 (2.31, 2.48)	0.44
Neutrophil-to-lymphocyte ratio (NLR)	2.46 (0.43, 0.77)	1.98 (0.33, 0.48)	0.02
Monocyte-to-lymphocyte ratio (MLR)	0.327 (0.28, 0.37)	0.326 (0.29, 0.35)	0.9
Platelet/lymphocyte ratio (PLR)	141.41 (127.47,	132.87 (124.54,	0.07

155.36)

141.2)

1 "n" sample size, % percentage

2 Chi-square test for categorical variables, and t-test numeric variables

Table.2 Regression analysis for predicting factors associated with change of dry AMDcases and controls (adjusted for age, gender)

Hematological parameters	dry AMD	Controls	p-values cases vs controls ¹
	Beta coefficient (β)	Standard error (SE)	
Red blood cells	- 0.09	0.06	0.17
Hemoglobin	0.02	0.02	0.33
Mean Corpuscular Hemoglobin	0.01	0.01	0.32
Mean corpuscular volume	0.005	1.09	0.99
White blood cells	0.25	0.53	0.91
Platelet	-0.03	0.04	0.96
Mean platelet volume	-0.05	0.12	0.66
Red cell distribution width	0.39	0.72	0.67
Mean corpuscular hemoglobin concentration	-0.02	0.02	0.79
Eosinophils	-0.01	0.11	0.86
Monocytes	0.001	0.02	0.96
Neutrophils	-0.02	0.05	0.61
Lymphocytes	0.05	0.04	0.21
Neutrophil-to-lymphocyte ratio (NLR)	-0.07	0.08	0.13
Monocyte-to-lymphocyte ratio (MLR)	-0.04	0.05	0.36
Platelet/lymphocyte ratio (PLR)	-0.09	0.05	0.07

¹ ANCOVA used to estimate differences in covariances across patients with dry AMD and controls, adjusted for age and gender, and the kruskal wallis test for non-normal numeric variables

Table.3 Regression analysis for predicting factors associated with change of dry AMD cases and controls (adjusted for age, gender)

	Cases of dry AMD vs controls		p-value cases vs controls ¹
	Beta coefficient (β)	Standard error (SE)	
Neutrophil-to-lymphocyte ratio (NLR)	-0.13	0.08	0.13
Age	0.67	0.31	0.03*
Gender			
Male	Reference	Reference	
Female	-0.17	0.072	0.016*

1 ANCOVA used to estimate differences in covariances across patients with dry AMD and without AMD, adjusted for age and gender,
*Statistically significant.

Figures

Figure 1

Analysis of covariance for NLR