


RESEARCH

Open Access



# Assessment of leukocyte and systemic inflammation index ratios in dyslipidemia patients with dry eye disease: a retrospective case–control study

Amani Y. Alhalwani<sup>1,2\*</sup> , Salwa Y. Hafez<sup>2,3</sup>, Nasser Alsubaie<sup>4</sup>, Khalid Rayani<sup>4</sup>, Yamin Alqanawi<sup>4</sup>, Ziyad Alkhomri<sup>4</sup>, Saden Hariri<sup>4</sup> and Shatha Jambi<sup>2,5</sup>

## Abstract

**Background** Dry eye disease (DED) is a complication of dyslipidemia (DLP) that is caused by metabolic syndrome and increased inflammation. This research aimed to assess leukocyte and systemic inflammation index ratios as potential biomarkers for systemic inflammation in dyslipidemia patients with dry eye disease (DLP-DED).

**Methods** Several blood biomarkers were studied in 32 patients with DLP-DED (study group) and 63 patients with DLP-only (control group). The evaluated blood biomarkers included specific systemic inflammation index ratios, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte and platelet ratio (NLPR), and lipid profiles, such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglyceride (TG), albumin (ALB), and C-reactive protein (CRP) levels.

**Results** Lymphocyte levels were significantly greater in the DLP-DED group than in the DLP-only group ( $P=0.044$ ). In addition, a significant negative correlation between HDL and the NLPR ( $P=0.007$ ;  $r=-0.428$ ) and a significant negative correlation between the serum ALB concentration and the PLR ( $P=0.008$ ;  $r=-0.420$ ) were identified as potential inflammatory predictors of DLP-DED.

**Conclusion** The findings of this study suggest that patients with DLP-DED may benefit from routine blood monitoring of their elevated lipid profile and blood inflammatory biomarkers, such as CRP, leukocytes, and systemic inflammation index ratios (NLR, PLR, MLR, and NLPR), to reduce the complications of DLP on ocular health. The correlation data suggest that the NLPR, PLR, serum ALB concentration, and serum HDL concentration may be valuable inflammatory biomarkers in DLP-DED patients. More research is required to ascertain the significance of the NLR, PLR, MLR, and NLPR and the additive role that leukocytes play.

**Keywords** Inflammatory blood biomarkers, Leukocytes, Systemic inflammation index ratios, Dyslipidemia, Dry eye disease

\*Correspondence:

Amani Y. Alhalwani  
halwania@ksau-hs.edu.sa

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

## Introduction

Dyslipidemia (DLP) is a chronic disease resulting from an imbalanced lipid profile characterized by elevated levels of low-density lipoprotein cholesterol (LDL) and triglycerides (TG) combined with low levels of high-density lipoprotein cholesterol (HDL) [1]. There are two classes of DLP: primary DLP (familial hypercholesterolemia), which is caused by genetic factors, and secondary DLP, which is influenced by many other factors, such as obesity and a sedentary lifestyle [2]. Earlier research revealed a strong connection between inflammatory biomarkers and DLP [3, 4]. DLP is a significant contributor to coronary artery disease [3]. In addition, DLP has been associated with chronic inflammatory diseases such as diabetes [5], thyroid disease [6], and dry eye disease (DED) [7]. DLP has a high prevalence worldwide; for instance, 19.7% of Korean adolescents, 27% of American adolescents, and 34% of Chinese adults have been reported to have DLP [8]. A national study revealed that 33.3% of Saudi Arabian adults, particularly males, experienced DLP [9]. Approximately 30% of Saudi adults are classified as overweight or obese; this classification reflects poor dietary habits and an unhealthy lifestyle, further increasing the risk of developing DLP [10].

Numerous investigations have indicated an association between DLP and DED [1, 10–15]. Studies have proposed that lipid composition changes in DLP patients may impact tear film stability and contribute to the development and progression of DED [16–18]. The lipid layer within the tear film is essential for preventing evaporation and sustaining ocular surface lubrication [19]. DLP, which in many cases is characterized by elevated cholesterol and triglyceride levels, can compromise the quality and quantity of lipids in tears, resulting in high levels of evaporation and discomfort. Recognition of the correlation between DLP and DED is crucial to ensure comprehensive patient care. Multiple investigations have revealed the occurrence of DLP and DED together, which has led to potential therapeutic strategies that target lipid irregularities to relieve DED symptoms [2, 20–22].

One of the primary risk factors for DLP is the inflammatory state associated with metabolic syndrome [23]. Previous studies have revealed a strong relationship between CRP levels and the severity of inflammatory diseases such as diabetes and atherosclerosis, and CRP has been proven to be the most significant predictor of the risk of future cardiovascular events [24, 25]. CRP is an acute-phase protein primarily secreted by hepatocytes in response to various pathophysiological conditions, including inflammation, as part of nonspecific innate physiological reactions [26]. In parallel, albumin is the most abundant plasma protein and possesses antioxidant properties that control several physiological responses in bodily fluids [27]. CRP and serum ALB levels are valuable

indicators of disease onset, progression, or stabilization. The associations between elevated levels of inflammatory markers, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and DLP have been established in many studies [28–30]. One study showed that low-density lipoprotein cholesterol (LDL) and LDL-C/SF were positively correlated with high levels of inflammatory indicators [31]. However, the mean LDL particle size and high levels of HDL were negatively correlated with high levels of inflammatory indicators [32]. Another study investigated the association between inflammatory markers and carotid atherosclerosis, which can be caused by DLP [33]. A significant positive correlation was detected between the levels of inflammatory markers and atherosclerosis markers, the carotid artery intima-media thickness (IMT), and the amount of carotid plaque. Moreover, ESR and CRP levels are significantly positively correlated with increased carotid artery IMT [33]. Additionally, leukocyte biomarkers, including neutrophil count [26], monocyte count [27], lymphocyte count [28], and platelet count [34], play a role in inflammation. There is substantial evidence that systematic indices obtained from calculating leukocyte ratios are more strongly associated with inflammatory diseases than are those obtained from leukocyte ratios alone. A recent novel marker of systematic inflammation is the monocyte-to-HDL ratio (MHR), which reflects the proinflammatory activity of monocytes and the anti-inflammatory effects of HDL [35]. A study in 2018 used the MHR and CRP level as markers of inflammation in patients with non-Sjögren syndrome dry eye (NSSDE) [35]. A group of 70 NSSDE patients were tested using a questionnaire about DED and the Schirmer 1 test while observing abnormal ocular surface staining patterns. In NSSDE patients, the mean MHR was  $12.4 \pm 7.7$  mg/dL, and the mean CRP was  $2.9 \pm 1.1$  mg/dL; both indicators were significantly greater in the NSSDE group than in the control group ( $7.7 \pm 5.4$  and  $1.2 \pm 0.6$  mg/dL, respectively). As a result, the MHR is a potential marker of systemic inflammation after the establishment of cutoff values and can be used in clinical settings [35]. Although neutrophils, lymphocytes, and platelets are cellular indicators of inflammation, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are considered more accurate markers of inflammation than single measures. The NLR and PLR are utilized in various cardiovascular diseases, cancers and immune-mediated disorders [36, 37]. A case-control study of proinflammatory markers revealed that individuals with DED exhibited greater NLRs than did healthy controls [38]. Another inflammatory marker, the systemic immune-inflammation index (SII), which is based on platelet counts and the NLR, was examined in a prospective study involving patients with DED compared with a healthy group. The study concluded that the DED

group had a greater SII, which suggested that the SII could consistently indicate inflammation levels in individuals with DED [39].

The monocyte-to-lymphocyte ratio (MLR) is a clinically wide-ranging peripheral blood biomarker linked to many diseases. Its advantages include being a simple, cost-effective, and reproducible marker [36]. A study by Amalia et al. reported strong associations between lipid profiles and inflammatory markers (MLR and NLR) in patients with diabetes and atherosclerotic cardiovascular disease [40]. Another study showed that the MLR is a better inflammatory predictor than the NLR in cardiovascular disease patients [41]. Furthermore, numerous studies have indicated that the neutrophil-to-lymphocyte and platelet ratio (NLPR) is a novel inflammatory marker and essential predictor of inflammation in several inflammatory diseases, including COVID-19 [42–44]. Few studies have examined the relationship between chronic diseases and dry eye disease using blood biomarkers, such as inflammation index ratios [45–47]. Additionally, a study in which the association between DED and lipid profiles was investigated revealed that the results of participants with DED were similar to the results of those diagnosed with DLP compared with the healthy group [48]. Moreover, a Korean study reported elevated cholesterol levels in individuals with DED, suggesting that there is a need for routine examinations of the eyes of patients diagnosed with DLP due to the strong association between the two conditions [49]. It was previously discovered that DLP can cause inflammation of the ocular glands. However, the relationship between DLP and the risk of DED morbidity has been poorly studied by measuring systemic inflammation index ratios. This study aimed to determine potential novel biomarkers for DED progression in patients with DLP by investigating systemic inflammation index ratios (NLR, PLR, MLR, and NLPR) among patients with DLP-DED and patients with DLP-only.

## Method

### Study design

This study was based on a retrospective cross-sectional research model and convenient sampling methodologies. The data were collected from the Ministry of National Guard Health Affairs for all patients who had confirmed DLP with DED (study group) and DLP only (control group) between 2016 and 2023 in outpatient communities in Jeddah, Saudi Arabia. The participants' information was obtained from Bestcare's electronic medical records system.

### Population information

The required sample size was calculated using the clinical sample size calculator on the website <http://www.raosoft.com/samplesize.html>.

According to previous studies, the prevalence of DLP in DED patients is 40% [9]. The required sample size was calculated based on this prevalence and at a 95% confidence level, with a margin of error of  $\pm 5\%$ . The required minimum sample size was determined to be 360. Based on the available bestcare data, 95 patients who satisfied the inclusion criteria were included in the study.

### Laboratory findings

Laboratory blood tests were performed for parameters related to complete blood counts (CBCs), including neutrophil, lymphocyte, platelet, and monocyte counts; lipid profiles, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TG); and C-reactive protein (CRP) and albumin (ALB).

### Blood test calculations

The following systematic inflammation index ratios were subsequently calculated: the NLR, which was calculated by dividing the neutrophil count by the lymphocyte count [45]; the PLR, which was calculated by dividing the platelet count by the lymphocyte count [45]; the MLR, which was calculated by dividing the monocyte count by the lymphocyte count [50]; and the NLPR, which was calculated by dividing the neutrophil count by the lymphocyte count multiplied by the platelet count [44, 51].

### Participant groups and criteria

Patients were divided into a study group (DLP with DED; DLP-DED) and a control group (DLP-only) based on the principal indications for DLP. The number of DLP patients available in Bestcare's electronic medical records system influenced the sample size.

**The inclusion criteria** was adults aged  $\geq 18$  years. They could be of either gender. Patients with DLP were classified based on lipid profile tests, and patients with DED were classified based on ocular clinical assessments.

**The exclusion criteria** were patients who were under the age of 18 years, smokers, who were wearing contact lenses, who had undergone eye surgery, and who had other chronic diseases such as cancer.

### Statistical analysis

PRISM software (GraphPad Inc., San Diego, CA, USA) was used for data processing and analysis. Categorical variables are expressed as percentages, and numerical variables are presented as the mean and standard deviation (mean  $\pm$  SD).

A normality test, the Shapiro–Wilk test, was performed for nonparametric data ( $P$  value  $< 0.05$ ); thus, the Mann–Whitney test was subsequently employed to identify significant differences between the groups. A chi-square test

was used for categorical data (gender). Spearman's correlation tests were used to compare the levels of HDL, ALB, and CRP with those of the inflammatory biomarkers PLR and NLPR for both groups (DLP-DED and DLP-only). A  $P$  value  $<0.05$  was considered to indicate statistical significance.

### Ethical consideration

The study was approved by the ethics committee of the institutional review board of King Abdullah International Medical Research Centre (IRB approval number: IRB/166/23, and study number: RSS23J/007).

### Results

Two groups of participants were considered from the sample used in this study: the DLP-DED study group ( $n=32$ ) and the DLP-only control group ( $n=63$ ). The DLP-DED group comprised 62.5% males and 37.5% females, while the DLP-only group comprised 50.6% males and 49.4% females. There was no statistically significant difference between the groups ( $P=0.259$ ) according to the Mann-Whitney test. The average age for the DLP-DED group was  $60.0 \pm 11.6$  years, and that for the DLP-only group was  $51.55 \pm 16.05$  years. The difference in age between the two groups was statistically significant ( $P=0.005$ ), as shown in Table 1.

The CRP level was lower in the DLP-DED patients ( $3.53 \pm 4.82$  mg/L) than in the DLP-only patients ( $3.91 \pm 4.79$  mg/L), but the difference was not statistically significant ( $P=0.388$ ). The albumin concentration in the

DLP-DED patients was  $43.63 \pm 3.82$  g/L lower than that in the DLP-only patients ( $44.24 \pm 3.67$  g/L) ( $P=0.235$ ), as shown in Table 1.

The leukocyte count biomarker that showed a statistically significant difference was the lymphocyte count in patients with DLP-DED, which was greater ( $2.673 \pm 0.95$ ) than that in DLP-only patients ( $2.26 \pm 0.85$ ). The difference was statistically significant ( $P=0.044$ ) (Table 1). The remaining leukocyte count biomarkers were not significantly different between patients with DLP-DED and those with DLP-only, as shown in Table 1.

The platelet count ( $\times 10^9/L$ ) for the DLP-DED patients was greater, at  $277.2 \pm 73.65$ , than that for the DLP-only patients, at  $264.1 \pm 70.16$  ( $P=0.217$ ). The neutrophil count ( $\times 10^9/L$ ) was lower in DLP-DED patients ( $3.72 \pm 1.21$ ) than in DLP-only patients ( $3.74 \pm 2.27$ ) ( $P=0.136$ ). The monocyte counts ( $\times 10^9/L$ ) were greater in the DLP-DED patients than in the DLP-only patients ( $0.54 \pm 0.18$  and  $0.52 \pm 0.20$ , respectively) ( $P=0.205$ ), as shown in Table 1.

In terms of systematic inflammation index ratios, the NLR, PLR, MLR, and NLPR were all lower in DLP-DED patients than in DLP-only patients, but the differences were not statistically significant: NLR,  $1.50 \pm 0.60$  versus  $2.10 \pm 2.28$  ( $P=0.491$ ); PLR,  $113.1 \pm 42.77$  versus  $132.0 \pm 69.9$  ( $P=0.094$ ); MLR,  $0.22 \pm 0.11$  versus  $0.27 \pm 0.20$  ( $P=0.188$ ); and NLPR,  $0.006 \pm 0.003$  versus  $0.008 \pm 0.009$  ( $P=0.279$ ), respectively, as shown in Table 1.

Regarding the lipid profiles, DLP-DED and DLP-only patients showed high or borderline levels compared to the normal test range. The HDL, LDL, TC, and TG values (mmol/L) for the DLP-DED patients versus DLP-only patients were not significantly different: HDL,  $1.28 \pm 0.32$  versus  $1.25 \pm 0.36$  ( $P=0.327$ ); LDL,  $2.82 \pm 0.84$  versus  $3.16 \pm 1.63$  ( $P=0.379$ ); TC,  $4.74 \pm 0.97$  versus  $5.00 \pm 1.60$  ( $P=0.341$ ); and TG,  $1.34 \pm 0.82$  versus  $1.20 \pm 0.57$  ( $P=0.460$ ), as shown in Table 1.

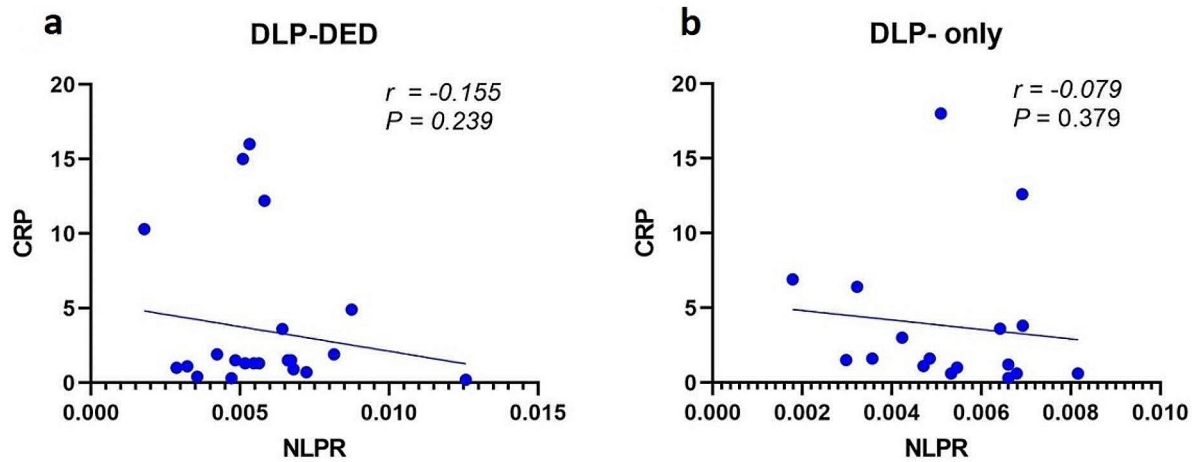
In DLP-DED patients, Spearman's correlation analysis revealed a significant negative correlation between CRP and the NLPR ( $P=0.239$ ;  $r=-0.155$ ) (Fig. 1a). In the DLP-only patients, there was no significant negative correlation between CRP and the NLPR ( $P=0.379$ ;  $r=-0.079$ ) (Fig. 1b).

For the DLP-DED patients, Spearman's correlation analysis demonstrated a positive correlation with no statistically significant difference between HDL values and the PLR ( $P=0.231$ ;  $r=0.134$ ) (Fig. 2a) but a negative correlation with a statistically significant difference between HDL values and the NLPR ( $P=0.007$ ;  $r=-0.428$ ) (Fig. 2b). Additionally, there was a significant negative correlation between the serum ALB concentration and the PLR ( $P=0.008$ ;  $r=-0.420$ ) (Fig. 2c), but there was no significant positive correlation between the serum ALB concentration and the NLPR ( $P=0.373$ ;  $r=0.059$ ) (Fig. 2d).

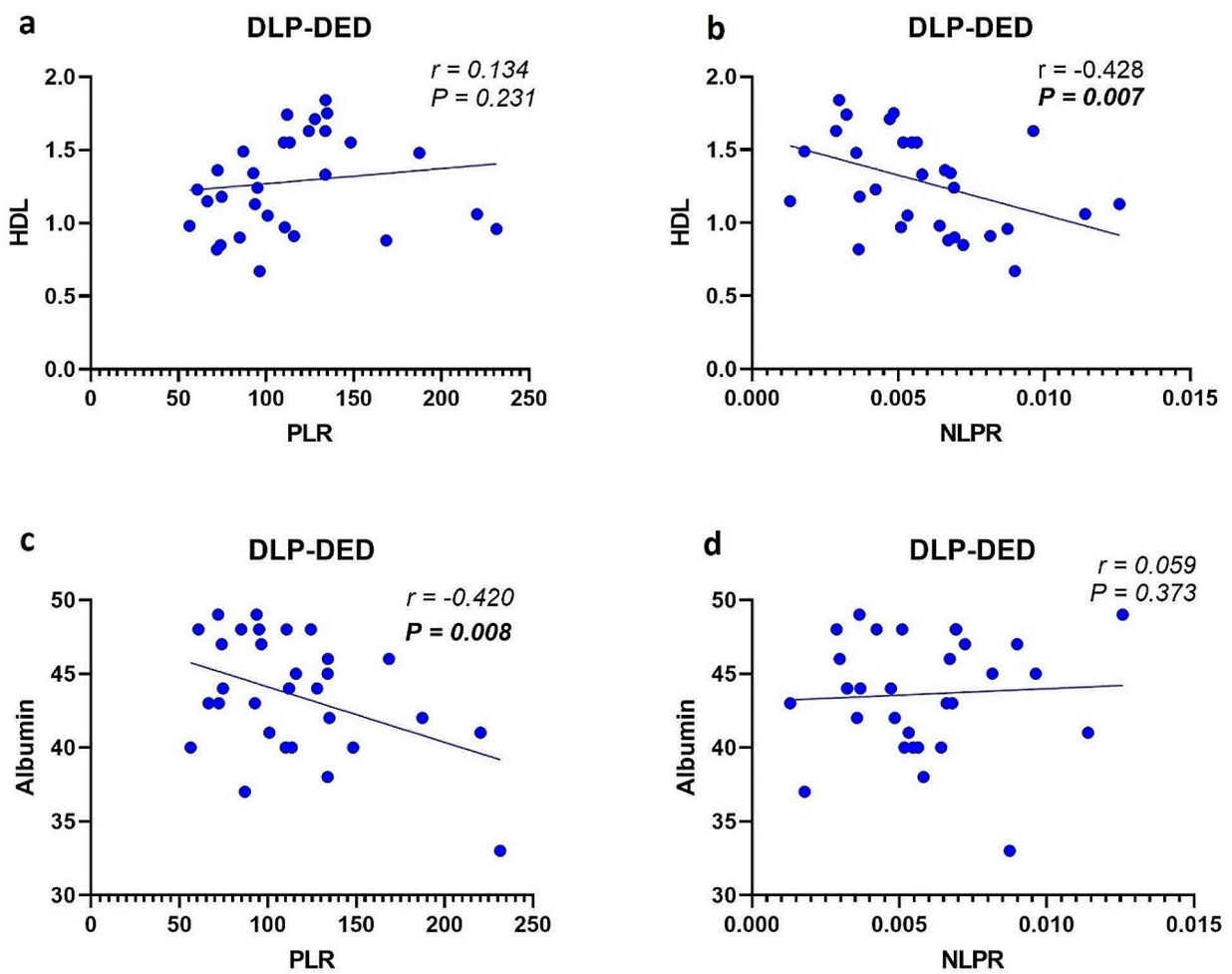
**Table 1** Comparison of demographic data and laboratory findings between DLP-DED patients and DLP-only patients

Variable	DLP-DED (mean $\pm$ SD)	DLP-only (mean $\pm$ SD)	P-value
Age (years)	$60.0 \pm 1.60$	$51.5 \pm 16.05$	<b>0.005</b>
CRP (mg/L)	$3.53 \pm 4.82$	$3.91 \pm 4.79$	0.388
Albumin (g/L)	$43.0 \pm 3.82$	$44.24 \pm 3.67$	0.235
Platelet count $\times 10^9/L$	$277.2 \pm 73.65$	$264.1 \pm 70.16$	0.217
Lymphocyte count $\times 10^9/L$	$2.67 \pm 0.95$	$2.26 \pm 0.85$	<b>0.044</b>
Neutrophil count $\times 10^9/L$	$3.72 \pm 1.21$	$3.74 \pm 2.27$	0.136
Monocyte count $\times 10^9/L$	$0.54 \pm 0.18$	$0.52 \pm 0.20$	0.205
NLR	$1.50 \pm 0.60$	$2.10 \pm 2.28$	0.491
PLR	$113.1 \pm 42.77$	$132.0 \pm 69.9$	0.094
MLR	$0.22 \pm 0.11$	$0.27 \pm 0.20$	0.188
NLPR	$0.006 \pm 0.003$	$0.008 \pm 0.009$	0.279
HDL (mmol/L)	$1.28 \pm 0.32$	$1.25 \pm 0.36$	0.327
LDL (mmol/L)	$2.82 \pm 0.84$	$3.16 \pm 1.63$	0.379
TC (mmol/L)	$4.74 \pm 0.97$	$5.00 \pm 1.60$	0.341
TG (mmol/L)	$1.34 \pm 0.82$	$1.20 \pm 0.57$	0.460

The normal ranges of each parameter were as follows: CRP ( $<5$  mg/L), neutrophils ( $2-7.50 \times 10^9/L$ ), monocytes ( $0.2-0.8 \times 10^9/L$ ), platelets ( $150-450 \times 10^9/L$ ), lymphocytes ( $1.5-4.0 \times 10^9/L$ ), high-density lipoprotein (HDL) ( $1.55-1.10$  mmol/L), low-density lipoprotein (LDL) ( $<2.59$  mmol/L), total cholesterol (TC) ( $\sim 5.18$  mmol/L), triglyceride (TG) ( $<1.70$  mmol/L), and albumin (ALB) ( $35-55$  g/L). # Mann-Whitney test. Statistically significant values ( $P<0.05$ ) are shown in bold



**Fig. 1** Scatter plots of CRP versus the NLPR for DLP-DED (a) and DLP-only (b) patients



**Fig. 2** Scatter plots of HDL versus the PLR (a), HDL versus the NLPR (b), ALB versus the PLR (c), and ALB versus the NLPR (d), all for DLP-DED patients. Statistically significant values ( $P < 0.05$ ) are shown in bold



## Discussion

Although DLP has been well studied, few studies have examined other DLP-related conditions, including DED. Since DED is a multifactorial disease driven by inflammation and since DLP is a risk factor, more research is needed to improve its diagnosis, prognosis, and therapeutic planning. This retrospective study was designed to investigate the level of inflammation among patients with DLP-DED compared with DLP-only subjects by measuring the levels of leukocytes and systematic inflammation index ratios of blood biomarkers. In this study population, there were more males than females among the DLP-DED patients. However, there was no statistically significant difference between the two groups. This finding is consistent with previous research on sex differences in patients with DLP, which demonstrated that DLP was sex independent and was consistent with lipid profiles [11, 52–54]. In contrast, it influences the incidence of DED; studies have revealed that DED has a 17% greater chance of occurring in females than in males (11%) [55]. Gender also plays a role in the symptomatology of DED, as studies have shown that females, on average, have higher total symptom scores than males [56]. According to a meta-analysis, DLP and DED are significantly correlated, more so among females than males [21]. The demographic analysis in this study revealed an average age of 60 years in the DLP-DED patients, which reflected an older age group. This finding is consistent with earlier reports showing that DLP and DED are age dependent [1, 15, 57–59].

Remarkably, knowledge of the extent of inflammation can assist in limiting the etiology and decreasing the severity of health complications, which should help patients maintain and improve their quality of life. Systematic inflammatory blood biomarkers are used to assess the degree of inflammation in patients with chronic diseases. CRP is a well-known indicator of vascular inflammation linked to lipid abnormalities [26]. Another blood biomarker that is influenced by inflammation is albumin [60]. When CRP and ALB levels were compared in this study, there was no significant difference between the DLP-DED and DLP-only patients. This elevated level of inflammation in both groups indicates that it is related to DLP, suggesting that CRP and ALB are independent predictors of DED. The leukocyte count biomarkers, including neutrophils [26], monocytes [27], lymphocytes [28], and platelets [34], are essential predictors of inflammation. These leukocytes play a crucial role in the inflammatory process and are involved in various diseases [61, 62]. In this study, there were no significant differences in platelet, neutrophil, or monocyte counts between DLP-DED patients and DLP-only patients. However, there was a significant increase in the lymphocyte count in DLP-DED patients compared

with DLP-only patients. Previous research has indicated that lymphocytes and other immune cells are involved in inflammatory disorders such as DED [63]. This finding demonstrated that monitoring lymphocyte counts could indicate the development of DED in DLP patients.

Furthermore, this study examined potential novel biomarkers for DED associated with subclinical inflammation in patients with DLP. Data from this investigation showed that the ratios of systematic inflammation indices (NLR, PLR, MLR, and NLPR) were not significantly different between DLP-DED patients and DLP-only patients. Emerging research supports the use of the NLR and PLR as more reliable indicators of inflammation in many diseases than other indicators, such as neutrophil and platelet counts [64, 65]. One study revealed that DED patients consistently had greater NLR values than healthy subjects (controls) but that PLR values were unaffected [66]. Moreover, the NLR is greater in patients with chronic diseases than in those without chronic diseases. Alhalwani et al. demonstrated that individuals with type 2 diabetes and DED had higher NLRs than patients with DED alone, suggesting that the NLR could be a potential predictor of DED [67, 68]. Furthermore, these biomarkers were investigated by Ghobady et al. [44] and Hasanefendić et al. [69], and correlations between the NLR and PLR and inflammation were found. Growing evidence indicates a strong connection between DED and the severity of DLP [70]. The MLR has significant prognostic value in many studies, including studies on DLP, ischemic stroke, and coronary heart disease [70–72]. However, the MLR and DLP were not evaluated before this study. The NLPR is a recently developed inflammatory biomarker, and its correlation with DLP patients has not been thoroughly investigated. However, recent NLPR studies reported that the NLPR has prognostic value in several inflammatory diseases, including acute coronary syndrome [68], acute kidney injury [48, 69], and COVID-19 [71].

Epidemiological research indicates that elevated lipid profiles are a major factor in the development of several inflammatory diseases, including DED [1, 8, 48]. Here, the lipid profile varied slightly between the DLP-DED and DLP-only patients. This finding is in line with a study by Choi et al., which showed that hypercholesterolemia was substantially more common among DED patients, with a greater prevalence in those with severe DED. In the study by Choi et al., the only parameter that showed a discernible difference between those with and without DED was HDL; those with DED had higher mean HDL levels [72]. According to these findings, elevated lipid profiles in patients with DLP could be used to predict the risk of inflammation in DED patients. Lipid profile levels increased in both groups, but the differences were not statistically significant.

Interestingly, the DLP-DED and DLP-only patients demonstrated a negative correlation between CRP levels and the NLPR, which agrees with previous studies [73–75]. In addition, there was a negative correlation between the serum ALB concentration and the PLR in DLP-DED patients. This finding was consistent with that reported by Cao et al. [76]. Moreover, the positive correlation between HDL levels and the PLR and the negative correlation between HDL levels and the NLPR are in agreement with those reported by Türkkan et al. [77]. Since albumin levels and the NLPR demonstrated a positive correlation, this ratio could thus be an adequate inflammatory biomarker in combination with DLP to be used to monitor and predict the incidence and progression of DED in older adults.

One of the most critical discoveries presented here is the prognostic potential of dyslipidemia in dry eye disease patients through the correlation between the NLPR and CRP, ALB, HDL, and albumin. These results highlight that establishing routine systemic inflammation index ratios to identify DLP patients at greater risk of developing DED could be essential for slowing DED progression and protecting the ocular surface from permanent deterioration.

### Study strengths and limitations

Recognizing the correlation between DLP and DED is crucial for ensuring ocular health in DLP patients. This study investigated novel prognostic tools for systemic inflammation index ratios (NLR, PLR, MLR, and NLPR) that may find a place in clinical use and treatment management. However, this study had some limitations due to the retrospective nature of the study, which compared DLP-DED patients to DLP-only laboratory data that were unavailable from the hospital database, leading to a small sample size.

### Conclusion

Findings and observations from this investigation indicate that inexpensive indicators such as systemic inflammation index ratios (NLR, PLR, MLR, and NLPR) have the potential to function as inflammatory biomarkers to predict DED risk in DLP patients. This finding may aid in the early identification and treatment of DED in such patients. Overall, changes in inflammatory biomarkers are linked to the incidence and progression of DED. Hence, early monitoring of leukocytes and systematic inflammation index ratios may help lower the incidence of DED in DLP patients. Further research is required to identify additional biomarkers that could be useful for identifying and preventing DED in patients with DLP.

### Abbreviations

ALB	Albumin
CBC	Complete blood count

CRP	C-reactive protein
DED	Dry eye disease
DLP	Dyslipidemia
DLP-DED	Dyslipidemia with dry eye disease
ESR	Erythrocyte sedimentation rate
HDL	High-density lipoprotein cholesterol
IMT	Intima-media thickness
LDL	Low-density lipoprotein cholesterol
MHR	Monocyte-to-HDL ratio
MLR	Monocyte-to-lymphocyte ratio
NSSDE	Non-Sjögren syndrome dry eye
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
TC	Total cholesterol
TG	Triglyceride

### Acknowledgements

none.

### Author contributions

All authors have read and approved the final version of the manuscript. The corresponding author had full access to all the data collected in this study and accepted complete responsibility for the integrity of the data and the accuracy of the data analysis.

### Funding

The author(s) report no funding associated with the work featured in this article.

### Data availability

No datasets were generated or analysed during the current study.

### Declarations

The study did not include supporting sources or financial relationships.

### Statement of human rights

The study adhered to research ethics and ensured that human rights were protected. This was a retrospective case–control study that relied on chart reviews and involved no direct contact with the subjects. The research team ensured and maintained the privacy and confidentiality of the data collected throughout the study period.

### Transparency statement

Amani Alhalwani affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

### Consent for publication

Not applicable.

### Conflict of interest

The authors declare no conflicts of interest.

### Competing interests

The authors declare no competing interests.

### Author details

<sup>1</sup>College of Science and Health Professions, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

<sup>2</sup>King Abdullah International Medical Research Center, Jeddah, Saudi Arabia

<sup>3</sup>College of Nursing, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

<sup>4</sup>College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

<sup>5</sup>College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

Received: 21 February 2024 / Accepted: 4 June 2024

Published online: 11 June 2024

## 12. References

- Kopin L, Lowenstein CJ. Dyslipidemia. *Ann Intern Med*. 2017;167(11):ITC81–96.
- Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15(3):575–628.
- Bafei SEC, Zhao X, Chen C, Sun J, Zhuang Q, Lu X, et al. Interactive effect of increased high sensitive C-reactive protein and dyslipidemia on cardiovascular diseases: a 12-year prospective cohort study. *Lipids Health Dis*. 2023;22(1):95.
- Dongway AC, Faggad AS, Zaki HY, Abdalla BE. C-reactive protein is associated with low-density lipoprotein cholesterol and obesity in type 2 diabetic Sudanese. *Diabetes Metabolic Syndrome Obesity: Targets Therapy*. 2015;8:427–35.
- Wu L, Parhofer KG. Diabetic dyslipidemia. *Metab Clin Exp*. 2014;63(12):1469–79.
- Mavromati M, Jornayvaz FR. Hypothyroidism-Associated Dyslipidemia: potential molecular mechanisms leading to NAFLD. *Int J Mol Sci*. 2021;22(23).
- Yang W, Yang K, Pan Y, Wu S, Chen X, Shen L, et al. A literature-derived dataset on risk factors for dry eye disease. *Sci Data*. 2023;10(1):21.
- Hong N, Lin Y, Ye Z, Yang C, Huang Y, Duan Q, et al. The relationship between dyslipidemia and inflammation among adults in east coast China: a cross-sectional study. *Front Immunol*. 2022;13:937201.
- AlMuhaidib S, AlBuhairan F, Tamimi W, AlDubayee M, AlAqeel A, Babiker A, et al. Prevalence and factors associated with dyslipidemia among adolescents in Saudi Arabia. *Sci Rep*. 2022;12(1):16888.
- Pan L, Yang Z, Wu Y, Yin R-X, Liao Y, Wang J, et al. The prevalence, awareness, treatment and control of dyslipidemia among adults in China. *Atherosclerosis*. 2016;248:2–9.
- Kolovou GD, Anagnostopoulou KK, Damaskos DS, Bilianou HI, Mihas C, Mili-onis HJ, et al. Gender differences in the lipid profile of dyslipidemic subjects. *Eur J Intern Med*. 2009;20(2):145–51.
- Correa R, Wayar F, Reaven P, Corpas E. Dyslipidemia in the Elderly. *Endocrinology of Aging*; Elsevier; 2021. pp. 607–50.
- Vekic J, Stefanovic A, Zeljkovic A. Obesity and dyslipidemia: a review of current evidence. *Curr Obes Rep*. 2023;1–16.
- Alamri S, Almalki MD, Alotaibi WN, Althobaiti S. The prevalence of dyslipidemia in obese patients. *Int J Med Developing Ctries*. 2019;3(1):006–9.
- Kim K-i. Dyslipidemia in older adults and management of dyslipidemia in older patients. *J Lipid Atherosclerosis*. 2015;4(1):1–6.
- McCulley JP, Shine W. A compositional based model for the tear film lipid layer. A compositional based model for the tear film lipid layer. *Trans Am Ophthalmol Soc*. 1997;95:79–93.
- Osae EA, Steven P, Redfern R, Hanlon S, Smith CW, Rumbaut RE et al. Dyslipidemia and Meibomian Gland Dysfunction: utility of Lipidomics and experimental prospects with a Diet-Induced obesity mouse model. *Int J Mol Sci*. 2019;20(14).
- Chun YH, Kim HR, Han K, Park YG, Song HJ, Na KS. Total cholesterol and lipoprotein composition are associated with dry eye disease in Korean women. *Lipids Health Dis*. 2013;12:84.
- Tavares Fde P, Fernandes RS, Bernardes TF, Bonfioli AA, Soares EJ. Dry eye disease. *Semin Ophthalmol*. 2010;25(3):84–93.
- Dao AH, Spindle JD, Harp BA, Jacob A, Chuang AZ, Yee RW. Association of dyslipidemia in moderate to severe meibomian gland dysfunction. *Am J Ophthalmol*. 2010;150(3):371–5.
- Wang T-H, Tsai Y-J, Wang Y-H, Wu C-L, Lin I-C. Relationship between Dry Eye Disease and Dyslipidemia: a systematic review. *J Clin Med*. 2023;12(20):6631.
- Wang TJ, Wang IJ, Hu CC, Lin HC. Comorbidities of dry eye disease: a nationwide population-based study. *Acta Ophthalmol*. 2012;90(7):663–8.
- Blaton V. How is the metabolic syndrome related to the Dyslipidemia? *Ejifcc*. 2007;18(1):15–22.
- Swastini DA, Wiryanthini IAD, Ariastuti NLP, Muliantara A. Atherosclerosis prediction with high sensitivity C-reactive protein (hs-CRP) and related risk factor in patient with dyslipidemia. *Open Access Macedonian J Med Sci*. 2019;7(22):3887.
- Alhalwani AY, Baqar R, Algadaani R, Bamallem H, Alamoudi R, Jambi S et al. Investigating neutrophil-to-lymphocyte and C-Reactive protein-to-albumin ratios in type 2 Diabetic patients with Dry Eye Disease. *Ocul Immunol Inflamm*. 2023;1–7.
- Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Investig*. 2003;111(12):1805–12.
- Sheinenzon A, Shehadeh M, Michelis R, Shaoul E, Ronen O. Serum albumin levels and inflammation. *Int J Biol Macromol*. 2021;184:857–62.
- Szabó MZ, Szodoray P, Kiss E. Dyslipidemia in systemic lupus erythematosus. *Immunol Res*. 2017;65:543–50.
- Popadic V, Brajkovic M, Klasnja S, Milic N, Rajovic N, Lisulov DP, et al. Correlation of dyslipidemia and inflammation with obstructive sleep apnea severity. *Front Pharmacol*. 2022;13:897279.
- Dessein PH, Joffe BI, Stanwix A, Botha AS, Moomal Z. The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. *J Rheumatol*. 2002;29(3):462–6.
- Zhang Y, Li S, Xu R-X, Zhu C-G, Guo Y-L, Wu N-Q et al. Systemic inflammatory markers are closely associated with atherogenic lipoprotein subfractions in patients undergoing coronary angiography. *Mediators of Inflammation*. 2015;2015.
- Zhang Y, Li S, Xu R-X, Zhu C-G, Guo Y-L, Wu N-Q, et al. Systemic inflammatory markers are closely associated with atherogenic lipoprotein subfractions in patients undergoing coronary angiography. *Mediat Inflamm*. 2015;2015:235742.
- Del Rincón I, Williams K, Stern MP, Freeman GL, O’Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. *Arthritis Rheumatism: Official J Am Coll Rheumatol*. 2003;48(7):1833–40.
- Sonmez O, Sonmez M. Role of platelets in immune system and inflammation. *Porto Biomedical J*. 2017;2(6):311–4.
- PaşAoğlu Ö, PaşAoğlu H. Elevated monocyte to HDL ratio as a new inflammatory marker in patients with dry eye. *New Front Ophthalmol*. 2018;4(6).
- Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are predictors of Heart failure. *Arq Bras Cardiol*. 2015;105(6):606–13.
- Chen JH, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. *World J Gastroenterol*. 2017;23(34):6261–72.
- Meng Y-F, Pu Q, Ma Q, Zhu W, Li X-Y. Neutrophil/lymphocyte ratio as an inflammatory predictor of dry eye disease: a case-control study. *Ther Clin Risk Manag*. 2021;259–66.
- Ozarslan Ozcan D, Kurtul BE, Ozcan SC, Elbeyli A. Increased systemic immune-inflammation index levels in patients with dry eye disease. *Ocul Immunol Inflamm*. 2022;30(3):588–92.
- Amalia M, Saputri F, Sauriasari R, Widyantoro B. Complete blood count, lipid profiles, and inflammatory markers associated with atherosclerotic cardiovascular disease in patients with diabetes [version 1; peer review: awaiting peer review]. *F1000Research*. 2023;12(1470).
- Ji H, Li Y, Fan Z, Zuo B, Jian X, Li L, et al. Monocyte/lymphocyte ratio predicts the severity of coronary artery disease: a syntax score assessment. *BMC Cardiovasc Disord*. 2017;17:1–8.
- Damar Çakırca T, Torun A, Çakırca G, Portakal RD. Role of NLR, PLR, ELR and CLR in differentiating COVID-19 patients with and without pneumonia. *Int J Clin Pract*. 2021;75(11):e14781.
- Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The systemic inflammation index on admission predicts in-hospital mortality in COVID-19 patients. *Molecules*. 2020;25(23):5725.
- Ghobadi H, Mohammadshahi J, Javaheri N, Fouladi N, Mirzazadeh Y, Aslani MR. Role of leukocytes and systemic inflammation indexes (NLR, PLR, MLP, dNLR, NLPR, AISI, SIR-I, and SIR-II) on admission predicts in-hospital mortality in non-elderly and elderly COVID-19 patients. *Front Med*. 2022;9:916453.
- Alhalwani AY, Jambi S, Borai A, Khan MA, Almarzouki H, Elsayid M, et al. Assessment of the systemic immune-inflammation index in type 2 diabetic patients with and without dry eye disease: a case-control study. *Health Sci Rep*. 2024;7(5):e1954.
- Elbeyli A, Kurtul BE, Ozcan DO, Ozcan SC, Dogan E. Assessment of red cell distribution width, platelet/lymphocyte ratio, systemic immune-inflammation index, and neutrophil/lymphocyte ratio values in patients with central retinal artery occlusion. *Ocul Immunol Inflamm*. 2022;30(7–8):1940–4.
- Yılmaz Tuğan B, Ergen A, Özkan B. Monocyte-to-high-density lipoprotein ratio and systemic immune-inflammation index: potential parameters for the evaluation of disease activity and severity in Graves’ ophthalmopathy? *Int Ophthalmol*. 2024;44(1):1–9.
- Rathnakumar K, Ramachandran K, Baba D, Ramesh V, Anebaracy V, Vidhya R, et al. Prevalence of dry eye disease and its association with dyslipidemia. *J Basic Clin Physiol Pharmacol*. 2018;29(2):195–9.
- Chun YH, Kim HR, Han K, Park Y-G, Song HJ, Na K-S. Total cholesterol and lipoprotein composition are associated with dry eye disease in Korean women. *Lipids Health Dis*. 2013;12(1):1–8.



50. Alfihli MA, Alsughayyir J, Basudan AM, Alsubki R, Alqahtani S, Awan ZA, et al. editors. Monocyte–lymphocyte ratio and dysglycemia: a Retrospective, cross-sectional study of the Saudi Population. *MDPI*; 2022.
51. Li Y, Zou Z, Zhang Y, Zhu B, Ning Y, Shen B, et al. Dynamics in perioperative neutrophil-to-lymphocyte\* platelet ratio as a predictor of early acute kidney injury following cardiovascular surgery. *Ren Fail.* 2021;43(1):1012–9.
52. Kolovou GD, Anagnostopoulou K, Pilatis N, Kafaltis N, Sorodila K, Psarros E, et al. Fasting serum triglyceride and high-density lipoprotein cholesterol levels in patients intended to be treated for dyslipidemia. *Vasc Health Risk Manag.* 2005;1(2):155–61.
53. Kolovou GD, Anagnostopoulou K, Pilatis N, Kafaltis N, Sorodila K, Psarros E, et al. Low fasting low high-density lipoprotein and postprandial lipemia. *Lipids Health Dis.* 2004;3(1):1–8.
54. Rubins HB, Davenport J, Babikian V, Brass LM, Collins D, Wexler L, et al. Clinical Investigation and Reports-Reduction in Stroke with Gemfibrozil in Men with Coronary Heart Disease and low HDL cholesterol: the Veterans affairs HDL intervention trial (VA-HIT). *Circulation-Hagerstown.* 2001;103(23):2828–33.
55. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol.* 2000;118(9):1264–8.
56. Vehof J, Smitt-Kamminga NS, Nibourg SA, Hammond CJ. Sex differences in clinical characteristics of dry eye disease. *Ocul Surf.* 2018;16(2):242–8.
57. The Epidemiology of Dry Eye Disease: Report of the Epidemiology Subcommittee of the International Dry Eye Workshop. (2007). *The Ocular Surface.* 2007;5(2):93–107.
58. Ferdinand KC. Ethnic, gender, and age-related differences in the treatment of dyslipidemia. *Am J Manag Care.* 2006;12(5):S400–4.
59. Ding J, Sullivan DA. Aging and dry eye disease. *Exp Gerontol.* 2012;47(7):483–90.
60. Kaysen GA. Biochemistry and biomarkers of Inflamed patients: why look, what to assess. *Clin J Am Soc Nephrol.* 2009;4(Supplement\_1).
61. von Brühl M-L, Stark K, Steinhart A, Chandraratne S, Konrad I, Lorenz M, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med.* 2012;209(4):819–35.
62. Parren PW, Warmerdam PA, Boeijs LC, Arts J, Westerdaal NA, Vlug A, et al. On the interaction of IgG subclasses with the low affinity fc gamma RIIa (CD32) on human monocytes, neutrophils, and platelets. Analysis of a functional polymorphism to human IgG2. *J Clin Investig.* 1992;90(4):1537–46.
63. Vázquez-Mendoza A, Vannan D, Morales EG, González MI, Hernández JLR. Lymphocytes in Dry Eye Disease: IntechOpen London, UK; 2021.
64. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes.* 2017;10(1):12.
65. Abdallah AI, Abdelaziz AA, El-Sayed E-SE-M, Emran TM. Study of neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) as a predictor inflammatory marker for diabetic nephropathy in type 2 diabetic patients. *Egypt J Hosp Med.* 2018;72(7):4800–7.
66. Celik T. Assessment of Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with Dry Eye Disease. *Ocul Immunol Inflamm.* 2018;26(8):1219–22.
67. Alhalwani AY, Abudawood K, Qadizadah ABEA, Jambi S, Sannan NS. Immunoglobulin A levels and its correlation with neutrophil-to-lymphocyte ratio as inflammatory biomarkers for dry eye disease in type 2 diabetes: a retrospective study. *Front Immunol.* 14:1184862.
68. Meng YF, Pu Q, Ma Q, Zhu W, Li XY. Neutrophil/Lymphocyte ratio as an inflammatory predictor of Dry Eye Disease: a case-control study. *Ther Clin Risk Manag.* 2021;17:259–66.
69. Hasanefendić B, Šeherćehajić E, Dedić A, Tihčić-Kapidžić S, Begović E, Hajro S, et al. Systemic inflammatory indexes (NLR, DNLR, PLR and SII) role in predicting COVID-19 progression. *J Health Sci.* 2023;13(2):113–7.
70. Rhee MK, Mah FS. Inflammation in dry eye disease: how do we break the cycle? *Ophthalmology.* 2017;124(11):S14–9.
71. Nooh HA, Abdellateif MS, Refaat L, Kandeel EZ, Bayoumi A, Samra M, et al. The role of inflammatory indices in the outcome of COVID-19 cancer patients. *Med Oncol.* 2022;39:1–14.
72. Choi HR, Lee JH, Lee HK, Song JS, Kim HC. Association between dyslipidemia and dry eye syndrome among the Korean middle-aged population. *Cornea.* 2020;39(2):161–7.
73. Eissa M, Shaarawy S, Abdellateif MS. The role of different inflammatory indices in the diagnosis of COVID-19. *Int J Gen Med.* 2021;7843–53.
74. Harnoto YO, Assagaf A, Pratiwi DIN, Isa M, Nurasyidah I, Kusumawardhani E. The Influence of inflammatory factors (IL-6, CRP, NLPR, D-Dimer, LDH) on the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, in patients with severe and critical degrees of COVID-19. *Medica Hospitalia: Journal of Clinical Medicine.* 2023;10(3):352-8.
75. Li S, Yu S, Qin J, Peng M, Qian J, Zhou P. Prognostic value of platelet count-related ratios on admission in patients with pyogenic liver abscess. *BMC Infect Dis.* 2022;22(1):1–8.
76. Cao X, Zhao M, Li H, Xu D, Li M, Zhang X, et al. Three new inflammatory markers C reactive protein to albumin ratio, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio correlated with relapsing polychondritis disease activity index. *Clin Rheumatol.* 2021;40(11):4685–91.
77. Türkkän E, Dağ NÇ, Arabacı Ç, Dikler O, Dağ H. Evaluation of inflammatory hematological ratios (NLR, PLR, MLR and Monocyte/HDL-Cholesterol ratio) in obese adolescents. *Iberoamerican J Med.* 2022;4(1):11–7.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.