

## REFERENCE VALUES OF NEUTROPHIL LYMPHOCYTE RATIO AND PLATELET LYMPHOCYTE RATIO IN HEALTHY ADULTS IN A TERTIARY CARE CENTER IN NORTH INDIA

RAJAT JHAMB<sup>1</sup>, ROSHAN KUMAR<sup>1\*</sup>, PRIYANKA GOGOI<sup>2</sup>, G. S. RANGA<sup>1</sup>  
AND BINEETA KASHYAP<sup>3</sup>

<sup>1</sup>Department of Medicine, UCMS & GTB Hospital, New Delhi, India.

<sup>2</sup>Department of Pathology, UCMS & GTB Hospital, New Delhi, India.

<sup>3</sup>Department of Microbiology, UCMS & GTB Hospital, New Delhi, India.

Email: roshans118@gmail.com

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### ABSTRACT

**Background:** Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) have been suggested as easily measurable and less invasive marker with predictive and prognostic implications in various inflammatory and ischemic conditions. The studies showing the role of NLR and PLR as a predictive prognostic factor in several inflammatory and ischemic conditions have their cut-off value based on the median, higher quartile, or values determined using receiver-operating curves. Also, their values have been postulated to have geographical, racial, gender, and age differences. A standardized reference value of these attributes is therefore needed to put the results of previous studies into a context that allows for proper interpretation of their potential clinical value.

**Objectives:** To establish the reference values for Neutrophil-lymphocyte ratio (NLR) and Platelet-lymphocyte ratio (PLR) in healthy adults in a tertiary care center in North India.

**Methods:** 500 apparently healthy volunteers aged 18-60 years were enrolled for the study and their blood samples were analyzed by an automated counter (MinDr.ay Bc-6800) to get complete hemogram values. Neutrophil Lymphocyte Ratio (NLR) was calculated by dividing absolute neutrophil count by absolute lymphocyte count, likewise, Platelet Lymphocyte ratio (PLR) was calculated by dividing platelet count by absolute lymphocyte count.

**Results:** The mean NLR and PLR in our study were  $1.9 \pm 0.6$  and  $91.77 \pm 26.95$ , respectively. The mean NLR was  $1.88 \pm 0.61$  in males and  $1.93 \pm 0.59$  in females (P-value = 0.373). The mean PLR was  $91.55 \pm 27.49$  in males and  $92.08 \pm 26.24$  in females (P-value = 0.834). The mean NLR for different age groups was  $1.87 \pm 0.60$ ,  $1.93 \pm 0.62$ , and  $1.90 \pm 0.58$  in 18-30, 31-45, and 46-60 years respectively (P-value 0.584). The mean PLR was  $92.53 \pm 27.98$ ,  $90.54 \pm 26.53$ , and  $92.61 \pm 25.75$  in 18-30, 31-45, and 46-60 years age groups respectively (P-value = 0.735).

**Conclusion:** We propose a normal NLR and PLR to be  $1.9 \pm 0.6$  and  $91.77 \pm 26.95$  respectively in our population of North India with no significant difference between males and females. Also, we conclude that NLR and PLR do not differ with age. But more studies with a larger number are required to delineate the difference of NLR and PLR as per sex and age-group is concerned.

Keywords: Reference values; neutrophil lymphocyte ratio; NLR; platelet lymphocyte ratio; PLR.

### INTRODUCTION

The neutrophil lymphocyte ratio (NLR) and Platelet lymphocyte ratio (PLR) can be measured as a ratio of neutrophil to lymphocyte and ratio of platelet to

lymphocyte respectively. NLR and PLR are simply measurable, cost-effective, and easily available parameters that can reflect the intensity of stress or systemic inflammation. They have been evaluated in various studies as having a predictive and

prognostic role in different inflammatory and ischemic conditions such as shock, major surgery, sepsis, ischemic cardiac diseases, malignancy, and renal diseases [1–5].

The neutrophil lymphocyte ratio (NLR) has also been shown to be effective in predicting the prognosis of cancer treatments, coronary interventions, coronary artery bypass grafting, and Alzheimer's disease [3,4,6,7]. Increased NLR correlates with poor prognosis in certain gynecological cancers, gastrointestinal cancers, cardiovascular diseases, and sudden idiopathic sensorineural hearing loss [3,4,8,9].

Likewise, platelet lymphocyte ratio (PLR) has also been shown to be useful in estimating the degree of systemic inflammation and it also correlates with prognosis in various diseases like myocardial infarction, critical limb ischemia, end stage renal failure, and malignancies. Elevated values of PLR have been shown to confer poor prognosis in these conditions [10–14].

Since the values of NLR and PLR can be derived by a simple and inexpensive blood test i.e. complete blood count, these markers can be widely applied in our clinical practice. As per the available literature, many differences exist in these markers depending on age, sex, and race [15].

The study was conducted with the following objectives:

## **OBJECTIVES**

### **Primary Objective**

To establish the reference values for NLR and PLR in healthy adults.

### **Secondary Objective**

To establish the sex-specific and age-specific reference values of NLR and PLR in healthy adults.

## **METHODS**

### **Study Setting**

The study was conducted in the Department of Medicine (OPDs and IPD) and the Pathology Department at UCMS and Guru Teg Bahadur Hospital, Delhi, India. Subjects were recruited during the period from November 2018-April 2020.

### **Study Design**

#### **Cross-Sectional Study:**

500 apparently healthy volunteers aged 18-60 years including patient's attendants and hospital staff were screened by history and examination, and those fulfilling the inclusion criteria were enrolled for the study.

#### **Inclusion Criteria**

- Age 18-60 years
- BMI 18-25
- Smoking index (<5 cigarettes/day)
- Alcohol index (<21 units/week)
- No evidence of any chronic medical illness (e.g. DM / Hypertension / Coronary artery disease / Chronic liver disease / Chronic kidney disease etc.) / malignancy / psychiatric illness as per the basis of history, examination, and routine blood investigation.
- No evidence of any acute or chronic infection as per the basis of history, examination, and routine blood investigation.
- No history of any chronic medicine intake

### Estimation of NLR and PLR

Following strict sterile precautions, a 3ml sample of the peripheral venous sample was collected in an EDTA vial and the sample was subjected to analysis on an automated counter (Mindray Bc-6800). Complete hemogram values were obtained along with the absolute neutrophil count, absolute lymphocyte count, and platelet count. Neutrophil Lymphocyte Ratio (NLR) was calculated by dividing absolute neutrophil count by absolute lymphocyte count, likewise, Platelet Lymphocyte ratio (PLR) was calculated by dividing platelet count by absolute lymphocyte count.

### Statistical Analysis

The total number of participants included in the study was 500. Data were entered in a Microsoft Excel spreadsheet and after cleaning, the analysis was done for 466 participants using SPSS software version 20.0. Data were presented as mean and SD for continuous variables and percentages for categorical variables. Reference values of neutrophil lymphocyte ratio and platelet lymphocyte ratio, including age-specific and sex-specific ratios, were expressed as mean ± SD. The unpaired t test was done to compare two group means and the ANOVA test was done to compare means of more than two groups. P-Value of less than 0.05 was considered significant.

### RESULTS

The results obtained are summarized below:

#### Demographic Data

The total number of participants in the study were 466. The mean age of the study group was 34.90 ± 10.24 years. The study group was comprised of 271 (58.2%) males and 195 (41.8%) females.

#### Neutrophil Lymphocyte Ratio

The mean NLR in our study was 1.9±0.6. The mean NLR for different age groups was 1.87±0.60, 1.93±0.62, and 1.90±0.58 in 18-30, 31-45, and 46-60 years respectively (P-value0.584). The mean NLR was higher in females i.e., 1.93±0.59 compared to the mean NLR in males 1.88±0.61. But the difference didn't reach significance on applying unpaired t test (P-value = 0.373).

#### Platelet Lymphocyte Ratio

The mean PLR in our study was 91.77±26.95. The mean PLR for different age groups was 92.53±27.98, 90.54±26.53, and 92.61±25.75 in 18-30, 31-45, and 46-60 years age groups respectively (P-value = 0.735). The mean PLR was similar in males 91.55±27.49 and females 92.08±26.24 (P-value= 0.834).

**Table 1. Mean NLR and PLR in male and female and different age subgroups**

	Mean	Male	Female	18-30 yrs	31-45 yrs	46-60 yrs
<b>NLR</b>	1.9±0.6	1.88±0.61	1.93±0.59	1.87±0.60	1.93±0.62	1.90±0.58
		<b>P-value= 0.373</b>		<b>P-value= 0.584</b>		
<b>PLR</b>	91.77±26.95	91.55±27.49	92.08±26.24	92.53±27.98	90.54±26.53	92.61±25.75
		<b>P-value= 0.834</b>		<b>P-value= 0.735</b>		

## DISCUSSION

Recently there has been an immense interest in NLR and PLR as they have been shown to be independent prognostic markers for morbidity and mortality in certain conditions such as cancers and cardiovascular diseases [3,4,8,10]. NLR is also useful in the prediction and detection of inflammatory or infectious conditions and their postoperative complications [1,2,6]. The ease of availability of these parameters without additional cost to the patient may gradually replace the old markers of inflammation and malignancy.

Our results revealed the mean value of NLR in our area as  $1.9 \pm 0.60$ . A few studies have reported similar NLR in healthy individuals. Xiachun Meng et al. in a study at Henan, China gave a reference interval of NLR as 1.72(1.37,2.18), similarly, Luo et al who reported a mean NLR of 1.77 (0.88-4.0) [16]. Similarly, Jesse Fest et al study in the Rotterdam area, the Netherlands reported a mean NLR of 1.76 (0.83–3.92) and a study published in 2019 from Iran also reported a similar mean NLR of  $1.70 \pm 0.7$  [17,18]. Some studies from South America, North America, and Africa have shown higher normal NLR value. Huguet et al. study in Latin American noted the average value of NLR as 2.21 (median 1.91) which is higher than our study [19]. Azab et al study studied the mean NLR among 9427 samples in the U.S. National Health and Nutrition Examination Survey (NHANES), in this study, the mean NLR was found to be 2.15 [20]. Alexander NI et al study in North-central Nigeria reported an even higher mean value for NLR as 2.8(1.2-4.4) [21]. On the other hand, some studies from Europe and Asia have reported lower NLR than observed by us. In a study done by Forget et al in Belgium, the mean NLR was  $1.65 \pm 1.4$  [22] while Lee et al. from Seoul, South Korea reported a mean NLR

value of 1.65(0.11,3.19) which are lower than our study [15]. Similarly, a study published from Korea by Kweon et al study, where 83740 healthy subjects were evaluated for NLR, reported median NLR to be 1.53 similar to studies from China [23,24]. In an Indian study done in Chennai by Shiny et al, the mean NLR was reported to be  $1.5 \pm 0.41$  [25], while Acharya et al. reported the mean NLR as  $1.86 \pm 0.81$  from similar geographical zone [26]. Moreover, most of the Indian studies have reported mean NLR in healthy individuals by studying the control arm while evaluating the NLR in some diseases thus having a smaller sample size, thus questioning its statistical significance. These variations in the values of NLR may be an indication that race and environment affect the NLR.

As the age distribution is concerned in our study though NLR was higher in the age group 31-45 years ( $1.93 \pm 0.62$ ) and 46-60 years ( $1.90 \pm 0.58$ ) as compared to 18-30 years ( $1.87 \pm 0.60$ ) but the difference didn't reach any significance ( $P = 0.584$ ). Huguet et al. has reported variations in NLR in different decades of life, as has also been shown by Alexander NI et al. where Individuals of age 51 to 85 years had significantly higher NLR as compared to younger individuals of age 18 to 50 years ( $p=0.019$ ) [19,21]. Xiachun Meng et al. reported that the reference interval of NLR was significantly higher in age >65 years old [ $1.85(1.46-2.36)$ ] as compared to 18-65 years old [ $1.71(1.36-2.17)$ ]  $P < .001$  [16]. But contradictory to the above findings, Kweon et al. study observed an inverse relationship between NLR and age [23]. The findings in our study are contradictory to the above studies which can be explained by the fact that we included only healthy adults by excluding all the possible inflammatory and chronic conditions like diabetes, cardiovascular diseases, nephropathies,

obesity which are known to increase the NLR and as the age progresses the prevalence of cardiovascular diseases, malignancy, diabetes and other inflammatory conditions are known to rise.

In our study mean NLR though was higher in females i.e.  $1.93 \pm 0.59$ , compared to males  $1.88 \pm 0.61$  ( $P = 0.373$ ), but the difference didn't reach significance ( $P = 0.373$ ). Many studies have reported conflicting results regarding the difference in mean NLR between males and females with some investigators reporting higher NLR in males, while others finding no statistical significant difference and still others reporting higher NLR in females [16–18,20,21,23,24,27,28]. These variations in results may be due to confounding factors such as pregnancy, breastfeeding, intake of contraceptive pills which might affect NLR.

Our results revealed a mean value of PLR in our locality as  $91.77 \pm 26.95$ . Similar values for PLR have been reported by Luo et al. [99 (48-197)] [28]. A few studies from Asia have given a higher PLR value [16,18]. In a study by Lee et al from South Korea mean PLR was reported to be 132.40 (46.79-218.01) while Alexander NI et al from North Central Nigeria found the mean value PLR to be 137 (75-199) which are higher than our study [21,27]. In an Indian study done in South India by Acharya et al. mean PLR was reported to be  $111.6 \pm 37.36$  [26]. These variations in the values of PLR may be an indication that race and environment affect the PLR and also the inadequate sample size to reach a mean normal PLR.

In our study, the mean PLR for different age groups was  $92.53 \pm 27.98$ ,  $90.54 \pm 26.53$ , and  $92.61 \pm 25.75$  in 18-30, 31-45, and 46-60 years respectively. Though maximum PLR of  $92.61 \pm 25.75$  was seen in the age group 46-60 years, this difference didn't reach any

significance ( $P = 0.735$ ). Xiachun Meng et al reported that the reference interval of PLR was significantly higher in age >65 years old [139(116-169)] as compared to 18-65 year old [106(88-128)] ( $P < 0.001$ ) [16]. Alexander NI et al. study also suggested that Individuals aged 18 to 50 years had significantly lower PLR ( $p < 0.05$ ) than older individuals aged 51 to 85 years [21]. In contrast to the above studies, Luo et al. observed that with an increase in age the PLR tend to decrease and PLR is significantly higher in the young adults (18 - 64 years) than in old adults (65-79 years) ( $p < 0.001$ ) [28]. These conflicting results can be explained by the fact that we took only healthy individuals by screening to exclude all chronic conditions like hypertension, diabetes cardiovascular diseases which are known to increase the PLR.

In our study mean PLR was similar in males  $91.55 \pm 27.49$  and females  $92.08 \pm 26.24$  ( $P = 0.834$ ). Many studies have reported conflicting results regarding mean PLR between males and females. Some studies have reported higher mean PLR in females while Alexander NI et al reported higher mean PLR in males compared to females [16–18,21,24,27,28]. Kweon et al. didn't find any difference between sexes which is similar to our study [23]. The above findings can be explained by the fact, that in most of the studies confounding factors such as pregnancy, breastfeeding, intake of contraceptive pills have not been excluded, as was the case in our study.

To conclude, various studies done to comprehensively define the normal reference values of NLR and PLR have shown discrepancy and variable results as per mean NLR and PLR are concerned. Also, the variation in mean NLR and PLR with gender is discordant, with some studies showing higher NLR and PLR in males as compared to females and some studies

otherwise [16–18,20,21,23,24,27,28]. Also, the relation of NLR and PLR with age shown in studies is controversial with some studies showing the increase in NLR and PLR with age [16,21], few showing reverse association [23,28], and some showing bimodal curve especially in females [19].

Though in our study the sample size was adequate to get the reference range of NLR and PLR for a particular population but subgroup analysis like sex-wise difference or difference in different age groups could not be validated and require further studies with more subjects in each subgroup. Also, being a government hospital, which provides free treatment and caters mainly to people from lower socioeconomic strata, the impact of poor dietary habits i.e. low nutrients and antioxidants could be a confounding factor in the derivation of the normal reference range of NLR and PLR in our study.

## CONCLUSION

We propose a normal NLR and PLR to be  $1.9 \pm 0.6$  and  $91.77 \pm 26.95$  respectively in our population of North India with no significant difference between males and females. Also, we conclude that NLR and PLR don't differ with age. But more studies with a larger number are required to delineate the difference of NLR and PLR for subgroup analysis like sex and age-group.

### The main message of the article

- Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) have been suggested as easily measurable and less invasive markers with predictive and prognostic implications in various inflammatory and ischemic conditions.
- Their values have been postulated to have geographical, racial, gender, and age differences.

- A standardized reference value of these attributes is therefore needed to put the results of previous studies into a context that allows for proper interpretation of their potential clinical value.
- This study was conducted to establish the reference values for Neutrophil-lymphocyte ratio (NLR) and Platelet-lymphocyte ratio (PLR) in healthy adults in a tertiary care center in North India.
- The mean NLR and PLR in our study were  $1.9 \pm 0.6$  and  $91.77 \pm 26.95$ , respectively.

### Research questions

- Is there a relationship between NLR & PLR and the socioeconomic and dietary profile of an individual?
- Though in our study the sample size was adequate to get the reference range of NLR and PLR for a particular population but subgroup analysis like sex-wise difference or difference in different age-groups could not be validated and require further studies with more subjects in each subgroup.
- There are few studies in the Indian population giving NLR and PLR in various diseases and more studies need to be conducted for a better comparison of these markers in various inflammatory conditions after validation of reference values in a particular area as their values have been postulated to have geographical, racial and ethnic variations.

### CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## ETHICAL CLEARANCE

Ethical clearance was taken from Institutional Ethics Committee – Human Research (IEC-HR), UCMS.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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