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Association of neutrophil-lymphocyte ratio with metabolic syndrome and its components in Asian Indians (CURES-143)

Jayagopi Surendar, Karunakaran Indulekha, Viswanathan Mohan *, Rajendra Pradeepa

Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialities Centre, WHO Collaborating Centre for Non-communicable Diseases Prevention & Control, Gopalapuram, Chennai, India

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ABSTRACT

Background: Metabolic syndrome (MS) is the state of chronic low grade inflammation. This study looks at the relationship of neutrophil-lymphocyte ratio (NLR) in subjects with and without MS in Asian Indians.
Methods: Study subjects (n = 754) were recruited from the Chennai Urban Rural Epidemiology Study. MS was defined using the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) III criteria modified for waist according to World Health Organization Asia Pacific guidelines. A complete hemogram was done in all subjects using a five-part hematology analyzer (model SF-3000; Sysmex, Kobe, Japan). The NLR was calculated as the ratio between counts for neutrophils and total lymphocytes in subjects with (n = 422) and without (n 332) MS and correlated with number of metabolic abnormalities in those with MS.
Results: Subjects with five metabolic abnormalities had the highest NLR, and with decreasing number of metabolic abnormalities, the NLR decreased linearly (p for trend <0.001). Logistic regression analysis revealed that even after adjusting for age, gender and body mass index, MS was strongly associated with NLR ($p < 0.001$).
Conclusion: Among Asian Indians, NLR is correlated with MS and also with the number of metabolic abnormalities.

1. Introduction

The term metabolic syndrome (MS) refers to a constellation of several cardiometabolic abnormalities such as abdominal obesity, insulin resistance, hyperglycemia, hypertension and dyslipidemia. Several reports have shown that MS increases the risk of diabetes by 2 fold and that of CVD by 5 fold (Grundy, Cleeman, Daniels, et al., 2005; Kaur, 2014). According to estimates by the International Diabetes Federation (IDF) almost one quarter of the world's adult population has MS (International Diabetes Federation, n.d.). The prevalence of MS is reported to be high in Asian Indians (Enas, Mohan, Deepa, et al., 2007). A report showed that 25.8% of the general population and 50% of subjects with type 2 diabetes have MS (Deepa, Farooq, Datta, et al., 2007).

Numerous studies have shown an association of MS and insulin resistance (IR) with inflammation. Two hypotheses have been proposed to explain the relationship of MS with inflammation. The first states that chronic low-grade inflammation leads to metabolic disturbances, which in turn leads to IR (Fernández-Real & Ricart, 2003). The second suggests that altered glucose and lipid metabolism trigger inflammation which results in IR (Shoelson, Lee, & Goldfine, 2006). The relationship of systemic inflammatory markers high-sensitivity CRP (hs-CRP), TNF-α and IL-6 with MS and IR has been shown in several studies (Emanuela, Grazia, de Marco, et al., 2012; Gokulakrishnan, Deepa, Sampathkumar, et al., 2009; Gokulakrishnan, Deepa, Sampathkumar, et al., 2009). Further, these systemic markers act as strong prognostic factors for the future onset of diabetes and CVD. However, most of these markers are time consuming and expensive. Recently it has been shown that there is a strong relationship between white blood cells (Gokulakrishnan, Deepa, Sampathkumar, et al., 2009) and more specifically the ratio of neutrophils and lymphocytes (NLR) and several metabolic diseases, like diabetes and CVD (Bhat, Teli, Rijal, et al., 2013; Shiny, Bibin, Shanthirani, et al., 2014). NLR is also known to be associated with systemic pro-inflammatory cytokines (Guthrie, Charles, Roxburgh, et al., 2013; Kantola, Klintrup, Väyrynen, et al., 2012; Motomura, Shirabe, Mano, et al., 2013).NLR has been shown to be a more valuable marker for CVD than WBC, as it is less likely to be influenced by physiological conditions (Bhat et al., 2013). Estimation of NLR is attractive as it is easy to perform, readily available even at remote locations and is inexpensive. There is one report in a Turkish population showing an

Conflict of interest: None.

* Corresponding author at: Madras Diabetes Research Foundation & Dr. Mohans Diabetes Specialities Centre, WHO Collaborating Centre for Non-communicable Diseases Prevention & Control Gopalapuram, Chennai, 600 086, India. Tel.: +91 44 4396 8888; fax: +91 44 2835 0935.
E-mail address: drmohans@diabetes.ind.in (V. Mohan).
URL: http://www.drmohansdiabetes.com (V. Mohan).

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association of NLR with MS (Buyukkaya, Karakas, Karakas, et al., 2014). This study investigates the association of NLR with MS in Asian Indians, who are known to have an increased susceptibility to type 2 diabetes and premature coronary artery disease (Mohan, Sandeep, Deepa, et al., 2007).

2. Methodology

The study subjects were recruited from the Chennai Urban Rural Epidemiological Study (CURES), an epidemiological study conducted on a representative population (≥20 years old) of Chennai (formerly Madras), the fourth largest city in India. The methodology of the study has been published elsewhere (Deepa, Pradeepa, Rema, et al., 2003). In brief, 26,001 individuals were recruited for phase 1 of CURES, using a systematic random-sampling technique; subjects with self reported diabetes receiving treatment were classified as "known diabetes subjects." Fasting capillary blood glucose was determined using an OneTouch® Basic® glucometer (Lifescan, a Johnson & Johnson Company, Milpitas, CA) in all subjects. Details of the sampling are described in our website (www.drmohansdiabetes.com/bio/WORLD/pages/pages/ chennai.html). In phase 3 every 10th subject in phase 1 (n = 2600) was invited for clinical, biochemical, microvascular, and detailed eye examinations (Rema, Premkumar, Anitha, et al., 2005; Unnikrishnan, Rema, Pradeepa, et al., 2007). Phase 3 had a response rate of 90.4% (2350/2600 subjects participated). For the present study, every third subject from phase 3 of CURES (n = 783) maintaining the representative of CURES, was invited to participate and 761 participated (97.2% response rate). This included, 332 subjects without MS (non-MS group) and 422 subjects with MS (MS group). Subjects with infectious or inflammatory diseases and those on statins and asprins were excluded from the study.

Metabolic syndrome (MS) was defined according to the National Cholesterol Education Program–Adult Treatment Panel III criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) modified for waist according to World Health Organization Asia Pacific guidelines for obesity as shown below (World Health Organization & International Association for the Study of Obesity and International Obesity Task Force, 2000). MS was defined as the presence of any three of the following abnormalities: abdominal obesity defined as waist circumference ≥90 cm for men and ≥80 cm for women, high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg and/or on antihypertensive medications), elevated fasting glucose (fasting plasma glucose ≥100 mg/dL and/or on anti-diabetic medications), hypertriglyceridemia (≥150 mg/dl), or low high-density lipoprotein-cholesterol (<40 mg/dL for males and <50 mg/dL for females).

Table 1
Clinical and biochemical characteristics of study subjects.

Parameters	Non-MS (n = 332)	MS (n = 422)	p
Age [years]	45.3 ± 14.4	50.6 ± 10.6	<0.001
Gender (Male) (%)	61.2	49.2	0.001
Waist circumference [cm]	84.0 ± 10.6	92.2 ± 9.4	<0.001
Body mass index [kg/m^2]	23.3 ± 4.1	26.3 ± 4.0	<0.001
Systolic blood pressure (SBP) [mmHg]	117.7 ± 16.5	133.1 ± 12.1	<0.001
Diastolic blood pressure (DBP) [mmHg]	73.2 ± 10.3	79.0 ± 11.7	<0.001
Fasting plasma glucose [mg/dl]	111.9 ± 61.1	156.4 ± 66.7	<0.001
Glycated hemoglobin (HbA1c) [%]	6.8 ± 2.4	8.4 ± 2.3	<0.001
Total cholesterol [mg/dl]	100.1	175.5	<0.001
Serum triglycerides [mg/dl]*	110.9 ± 64.8	204.5 ± 147.0	<0.001
High density lipoprotein [HDL] cholesterol [mg/dl]	44.8 ± 10.7	39.2 ± 7.9	<0.001
Low density lipoprotein [LDL] cholesterol [mg/dl]	119.0 ± 36.5	122.4 ± 41.1	0.237
Microalbuminuria [mg/dl]	20.3 ± 38.7	36.4 ± 54.0	<0.001

* Values are expressed as geometric mean.

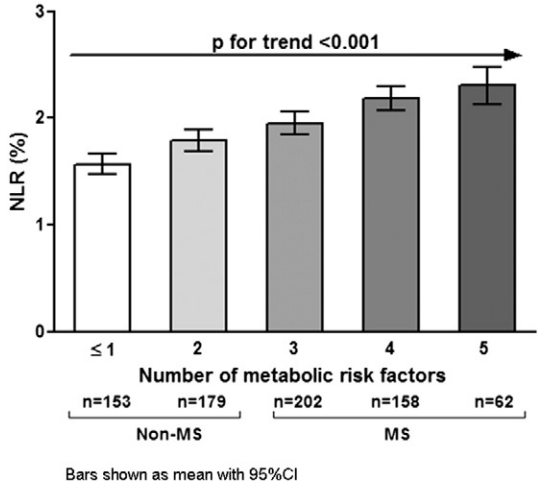


Fig. 1. NLR levels in relation to number of metabolic abnormalities.

Institutional ethical committee approval was obtained for the study, and informed consent was obtained from all the study subjects.

2.1. Anthropometric measurements

Anthropometric measurements, i.e. height, weight, and waist, were obtained using standardized techniques as detailed elsewhere (Deepa et al., 2003). Height was measured with a tape measured to the nearest centimeter. Weight was measured with a traditional spring balance that was kept on a firm horizontal surface. Waist was measured using a nonstretchable fiber measuring tape. The body mass index (BMI) was calculated as the weight (in kg) divided by the square of the height (in m). Blood pressure was recorded in the right arm in the sitting position to the nearest 2 mmHg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Industrial Electronic and Allied Products, Pune, India). Two readings were taken 5 min apart, and the mean of the two was taken as the blood pressure.

2.2. Biochemical parameters

Fasting plasma glucose (glucose oxidase–peroxidase method), serum cholesterol (cholesterol oxidase–peroxidase-amidopyrine-method), serum triglycerides (glycerol phosphate oxidase–peroxidase-amidopyrine-method), high-density lipoprotein-cholesterol (direct method; polyethylene glycol–pretreated enzymes), and creatinine (Jaffe's method) were measured using a Hitachi-912 Autoanalyzer (Boehringer Mannheim/Hitachi, Mannheim, Germany). The intra- and interassay coefficients of variation for the biochemical assays ranged between 3.1% and 7.6%. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Glycated hemoglobin (HbA1c) was estimated by high pressure liquid chromatography using a Variant machine (Bio-Rad, Hercules, CA). The intra- and interassay coefficients of variation of HbA1c were less than 10%.

2.3. Measurement of leukocyte count and NLR

Leukocyte count was assessed using a five-part hematology analyzer (model SF3000; Sysmex, Kobe, Japan) based on flow cytometry. The intra- and interassay coefficients of variation of the leukocyte count were <10%. NLR was calculated as the ratio between (i.e. percentage of) neutrophils and total lymphocyte counts in the study subjects.

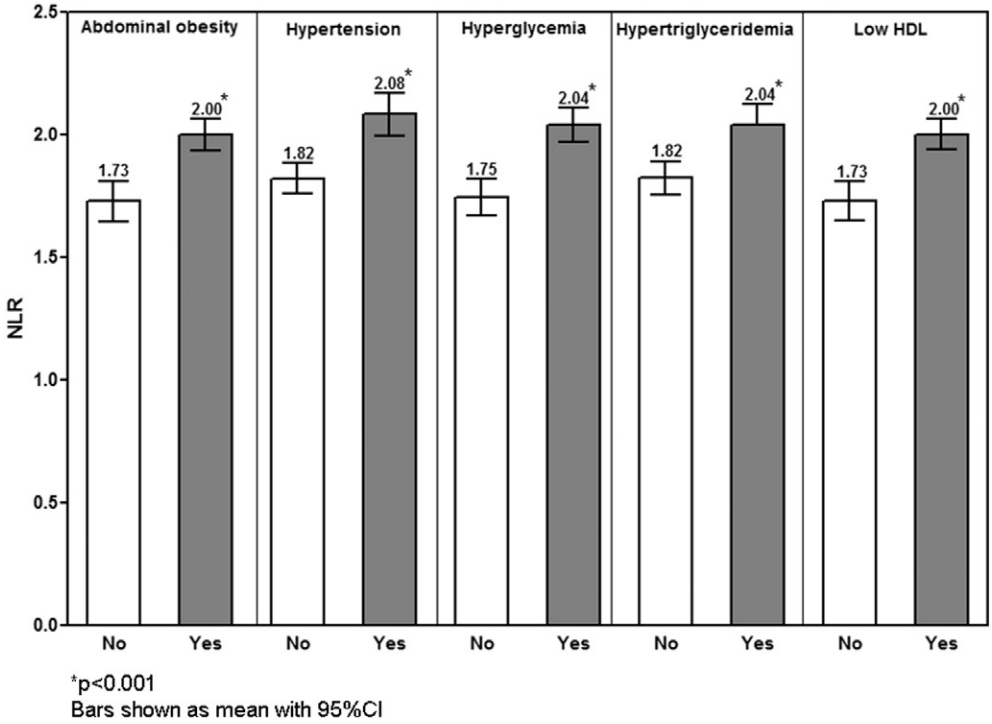


Fig. 2. Levels of NLR in relation to various components of MS in the study subjects.

2.4. Statistical analysis

Student's *t* test or one-way analysis of variance (with Tukey's HSD) as appropriate was used to compare groups for continuous variables, and x^2 test or Fisher's exact test was used to compare the proportions. Logistic regression analysis was done to look for association of NLR with MS after correcting for age, gender, and body mass index. The prediction ability of NLR to predict MS was examined by receiver-operating characteristic (ROC) curve analyses. All analyses were done using the Windows based SPSS statistical package (version 10.0, SPSS, Inc., Chicago, IL). $P < 0.05$ was considered as significant.

3. Results

Table 1 shows the clinical and biochemical characteristics of the study subjects. Compared to the non-MS subjects, the MS subjects were older ($p < 0.001$) and had higher body mass index ($p < 0.001$) and HbA1c ($p < 0.001$).

Fig. 1 shows that NLR was highest in participants with 5 metabolic risk factors (MRF) (2.31 ± 0.68) followed by 4 MRF (2.18 ± 0.69), 3 MRF (1.95 ± 0.74), 2 MRF (1.79 ± 0.68), and ≤1 MRF (1.57 ± 0.59) (p for trend <0.001) subjects.

Table 2
Association of NLR with metabolic syndrome.

Variables	Unadjusted OR (95% CI)	Adjusted for age and gender OR (95% CI)
NLR		
Metabolic risk factors		
Waist	1.83 (1.42–2.34)*	1.82 (1.41–2.35)*
Blood pressure	1.65 (1.33–2.03)*	1.59 (1.28–1.97)*
Fasting plasma glucose	1.87 (1.49–2.34)*	1.80 (1.43–2.27)*
Triglyceridemedia	1.53 (1.24–1.88)*	1.49 (1.21–1.84)*
High density lipoprotein	1.83 (1.43–2.34)*	1.87 (1.45–2.41)*
MS	2.48 (1.94–3.17)*	2.40 (1.87–3.08)*

* $p < 0.001$.

We next looked at each of the MRF separately. Participants with abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia and low HDL cholesterol showed increased NLR compared to the respective participants without these conditions ($p < 0.001$) (Fig. 2). Table 2 presents the results of the logistic regression analysis which shows that MS (odds ratio: 2.40, $p < 0.001$) and each component of MS ($p < 0.001$) showed a significant association with NLR even after adjusting for age, gender and BMI. As diabetes is one of the confounders which could influence NLR levels, we segregated the MS subjects based on their diabetes status. The NLR levels were not significantly different between diabetic and non-diabetic subjects ($p = 0.063$.)

Next we looked at the effect of gender. Differences in NLR levels between non-MS and MS subjects were compared and stratified based on gender. Both in males (MS: 2.10 ± 0.70 vs non-MS: 1.68 ± 0.63, $p < 0.001$) and females (MS: 2.08 ± 0.73 vs non-MS: 1.69 ± 0.66, $p < 0.001$) the NLR levels were significantly elevated in MS subjects. There was no significant difference in NLR levels between males and females with MS ($p = 0.806$) or non-MS ($p = 0.820$).

In order to investigate the impact of age on NLR levels, study subjects were categorized based on age. The NLR levels were significantly elevated in MS compared to non-MS subjects at all age groups. Among MS subjects, the NLR levels were not significantly different between the different age groups (p for trend 0.792) (Fig. 3).

Receiver operating characteristic (ROC) curves were constructed for obtaining (by maximizing the sensitivity and specificity) and the optimal cut-off point for NLR to predict MS was calculated (Fig. 4). The area under the ROC curve for NLR was 0.68 ($p < 0.001$), and a cut-point of 1.70 had the optimum sensitivity (67%) and specificity (63%) for predicting MS.

4. Discussion

The important observations of this study are as follows: NLR levels were higher in those with MS and higher in those with increasing number of metabolic abnormalities. MS and its components were

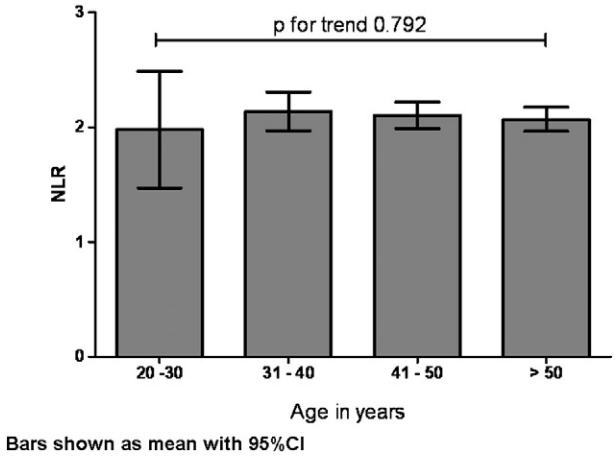


Fig. 3. Age wise NLR levels in MS subjects.

strongly associated with NLR even after adjusting for various confounders.

We have earlier reported increased levels of hs-CRP and WBC in subjects with MS and IR (Emanuela et al., 2012; Gokulakrishnan, Deepa, Sampathkumar, et al., 2009). Several studies have shown that NLR is a good marker for cardiovascular disease and solid tumors (Bhat et al., 2013; Templeton, McNamara, Šeruga, et al., 2014). Buyukkaya et al. (2014) showed that there is an elevation in NLR levels in MS subjects compared to controls and that a cut point of 1.84 predicted MS best in a Turkish population. Shiny et al. (2014) recently reportedan association of NLR with glucose intolerance. The utility of inflammatory markers as biomarkers appears to be ethnic specific and, a study done on hispanic and non-hispanic black and white subjects revealed that the mean values of NLR varied in different ethnic groups (Azab, Camacho-Rivera, & Taioli, 2014).

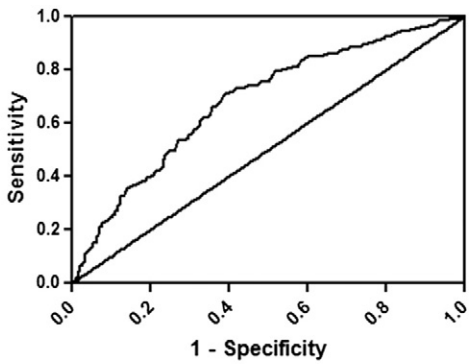
This study shows that an NLR cut point of 1.70 is associated with MS in our population. We also observed that NLR levels were higher in those with increasing number of metabolic abnormalities. The Prospective Metabolism and Islet Cell Evaluation (PROMISE) study showed that the association of NLR with insulin resistance was dependent on BMI (Lee, Harris, Retnakaran, et al., 2014). However, Ryder, Diez-Ewald, Mosquera, et al. (2014) reported that NLR was not associated with either obesity or insulin resistance. Our results show that 69% of hyperglycemic subjects, 78% of abdominally obese study and 78% of subjects with low HDL cholesterol fall under the 3rdtertile of NLR. These findings are similar to those of Imtiaz, Shafique, Mirza, et al. (2012) who showed that 66% of hypertensive subjects and 65% of diabetic individuals fall in the 3rd tertile of NLR.

NLR reflects the balance between two distinct but inter-connected arms of immune system, the innate and adaptive immunity. Neutrophils are the first cells that arrive at the site of infection/inflamed tissue which enable the recruitment of subsequent immune cells. Infiltration of neutrophils in adipose tissue was noticed in mice fed with high fat diet (HFD) even before macrophage infiltration and moreover the neutrophils were retained in the adipose tissue for a long time (Elgazar-Carmon, Rudich, Hadad, et al., 2008; Talukdar, Oh da, Bandyopadhyay, et al., 2012). Neutrophil elastase promotes IR by IRS 1 degradation and by inhibiting insulin stimulated AKT phosphorylation in liver and adipocytes (Talukdar et al., 2012). Metabolic conditions like hypercholesterolemia have also been shown to increase the systemic neutrophils (Drechsler, Megens, van Zandvoort, et al., 2010). In obesity, the levels of neutrophil secreting proteins (MPO and calprotectin) and activation of neutrophils are increased (Nijhuis, Rensen, Slaats, et al., 2009). Additionally, hyperglycemia is known to reduce the apoptosis of neutrophils and the levels of NLR were shown to decrease with improved glycemic control in subjects with diabetes (Sefil, Ulutas, Dokuyucu, et al., 2014).

Individuals with both diabetes and obesity are characterized by low lymphocyte counts (Shiny et al., 2014; Tanaka, Isoda, Ishihara, et al., 2001). This could be because the levels of DNA damage in circulatory lymphocytes, and their apoptosis rate, are enhanced in diabetes (Adaikalakoteswari, Rema, Mohan, et al., 2007; Otton, Soriano, Verlengia, et al., 2004). In addition, decreased proliferation rate of lymphocytes with decreased IL-2 receptor (which plays a pivotal role in lymphocyte differentiation and proliferation) has been observed in diabetes (Chang & Shaio, 1995). However, there are several subtypes of lymphocytes available and each subtype has a unique role in chronic metabolic diseases. Future studies should try to identify the association of neutrophils with specific lymphocytes in various metabolic conditions.

Due to the cross-sectional nature of our study, it is not possible to investigate any cause-effects relationships of NLR with MS. Prospective studies are needed to clarify this issue. Secondly, to determine their prognostic value, neutrophils should be measured repeatedly as they have a short life (7 h). Nevertheless, it is of interest that one study has reported that there was a strong relationship between the initial, last, maximum and average NLR levels, with mortality (Azab, Zaher, Weiserbs, et al., 2010).

In summary, this study suggests that a simple test, the NLR, has a significant association with MS in Asian Indians thus adding NLR to the long list of inflammatory markers associated with MS. Future research, through longitudinal and mechanistic studies, would help elucidate the temporal relationship between neutrophils and lymphocytes with MS and cardiovascular disease.



AUC (95% CI)	Cut point	Sensitivity (%)	Specificity (%)	p
0.68 (0.65-0.72)	>1.70	67	63	<0.001

Fig. 4. ROC curve of NLR with MS.

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