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Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea

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Abstract

There is a growing interest in research aimed at better understanding the disease status or predicting the prognosis of patients with simple blood tests associated with systemic inflammation. The neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) can be used as factors to determine the prognosis of patients in various clinical situations. However, reference values for these attributes based on large, healthy populations have yet to be determined.

From January 2014 to December 2016, data from routine blood analyses were collected from healthy patients in the checkup center of a tertiary hospital in Seoul, South Korea. Retrospective data review was then performed on an electronic medical record system. Data were treated anonymously as only age, sex, body mass index, medical history including cancer diagnosis, medications, and smoking status were considered. After the initial screen, we had a collection of 12,160 samples from patients without any medical history, including cancer treatment. This patient pool consisted of 6268 (51.5%, median age 47 years) and 5892 (48.5%, median age 46 years) male and female patients, respectively. The mean NLR across all ages was 1.65 (0.79), and the values for men and women were 1.63 (0.76) and 1.66 (0.82), respectively. The mean LMR, PLR, and MPV were 5.31 (1.68), 132.40 (43.68), and 10.02 (0.79), respectively. This study provides preliminary reference data on LMR, PLR, and MPV from different age and sex groups in South Korea. The results suggest that different cutoff values should be applied to the various patient populations.

Abbreviations: BMI = body mass index, IRB = Institutional Review Board, LMR = lymphocyte-monocyte ratio, MPV = mean platelet volume, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, SD = standard deviation.

Keywords: lymphocyte-monocyte ratio, mean platelet volume, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

1. Introduction

With the correlation between inflammatory status and disease or cancer prognosis, there is a growing interest in research aimed at better understanding the disease status or predicting the prognosis of patients with simple blood tests. The neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) can be used as factors to determine the prognosis of patients in various clinical situations.

The NLR, which can be measured in simple blood tests, is easily obtained, and determined in a cost-effective manner. As a marker of systemic inflammation, NLR has been shown to be effective in predicting the prognosis of cancer treatments, coronary interventions, coronary artery bypass grafting, and Alzheimer disease.[1–6] Likewise, the LMR, PLR, and MPV have been reported to measure the degree of systemic inflammation and indicate prognosis in critically ill patients during postoperative and intensive care.[7–9]

As a result, these markers can be easily applied in clinical practice. There is a possibility of identifying a disease or predicting health status using the NLR or other markers of the general population in healthy patients or those who are undiagnosed with disease. However, many differences exist in these markers depending on race, sex, and age. Currently, there is no standardized level of measurement demonstrating the significance of a value when it is higher than that of the average healthy patient. Therefore, the present study was designed to evaluate the sex- and age-specific reference values of NLR, LMR, PLR, and MPV according from blood samples taken from a healthy patient population.

2. Methods

This retrospective study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea (protocol number: 3-2016-0281; date of approval: December 2016). Because this was a retrospective study of data from precollected

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blood samples treated anonymously, the IRB gave a waiver for individual consent.

From January 2014 to December 2016, data from routine blood analyses were collected from healthy patients in the checkup center of a tertiary hospital in Seoul, South Korea. Hematologic measurements were conducted by the hospital clinical laboratory department, which performed internal quality controls at every 8 hours using calibrator XN-CAL and XN-CAL PT regularly, with XN-9000 automated hematology analyzers (Sysmex Corporation, Kobe, Japan). Between-assay coefficient of variation (%) of hematologic parameters were the 1.28 of white blood cell count, 1.99 of neutrophil %, 2.47 of lymphocyte %, and 3.93 of monocyte %. External quality assurance of this clinical laboratory was conducted by a government authorized organization, the *Korean* association of *quality assurance* for *clinical laboratories*.

Retrospective data review was then performed on an electronic medical record system. Data were treated anonymously as only age, sex, body mass index (BMI), medical history including cancer diagnosis, and smoking status were considered.

2.1. Statistical analysis

NLR was calculated by dividing neutrophil count by lymphocyte count. Same calculation method applied for other ratios which are LMR and PLR. After confirmation of a normal distribution, parameters were compared using independent samples test and intergroup comparison was performed using analysis of variance test. Relations in between data were analyzed with Pearson correlation analysis.

For the statistical analysis, SPSS 23.0 (SPSS Inc, Chicago, IL) software was used. P values $<.05$ were considered statistically significant.

3. Results

From January 2014 to December 2016, 20,122 patients visited the health checkup center of a tertiary hospital in Seoul, South Korea and received a routine blood analysis that included assessment of differential counts of white blood cells. After the initial data screen, we had a collection of 12,160 samples from patients without any medical history, including cancer treatment. The patient pool consisted of 6268 (51.5%, median age 47 years) and 5892 (48.5%, median age 46 years) males and females, respectively (Table 1). The number of patients according to BMI was also analyzed.

NLR, LMR, PLR, and MPV were analyzed based on sex and age (Table 2). Because all the data fit a normal distribution, we set

Table 1

Basic sample characteristics (n = 12160).

Variables	Categories	Subject tested
Sex	Male	6268 (51.5%)
	Female	5892 (48.5%)
Age, y	Male	46.64 (10.79)
	Female	45.99 (11.14)
BMI, kg/m^2	<18.5	633 (5.2%)
	18.5–24.9	8044 (66.15%)
	25–29.9	2931 (24.10%)
	>30	441 (3.63%)

Values are mean (SD), or number (proportion).
BMI = body mass index.

Table 2

Neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume representing reference value according to age.

	Total (mean ± 1.96 SD)		Age							
			–19	20–29	30–39	40–49	50–59	60–69	70–
NLR	1.65	F	1.662	1.654	1.736	1.765	1.754	1.481	1.493	1.618
	(0.107–3.193)		(0.064–3.260)	(0.326–2.982)	(−0.682–4.153)	(0.136–3.394)	(0.238–3.271)	(0.121–2.841)	(0.129–2.856)	(0.100–3.136)
		M	1.634	1.627	1.631	1.647	1.620	1.626	1.671	1.735
			(0.144–3.125)	(0.274–2.979)	(0.151–3.111)	(0.289–3.006)	(0.182–3.058)	(0.016–3.237)	(0–3.355)	(0.286–3.184)
LMR	5.31	F	5.598	5.498	5.595	5.476	5.243	6.081	5.920	5.476
	(2.008–8.612)		(2.130–9.067)	(2.219–8.778)	(1.953–9.237)	(2.095–8.857)	(2.067–8.418)	(2.481–9.681)	(2.356–9.483)	(2.157–8.794)
		M	5.048	4.870	4.957	5.042	5.147	5.042	4.823	4.596
			(2.000–8.096)	(1.374–8.366)	(2.023–7.891)	(1.995–8.088)	(2.161–8.134)	(1.980–8.104)	(1.502–8.143)	(1.752–7.440)
PLR	132.40	F	142.759	128.976	133.747	146.600	151.780	136.221	128.949	121.429
	(46.794–218.006)		(52.026–233.491)	(62.324–195.629)	(57.275–210.218)	(59.489–233.712)	(53.371–250.189)	(52.732–219.710)	(41.929–215.969)	(33.601–209.256)
		M	122.726	127.126	124.242	124.884	124.338	120.515	117.836	112.600
			(46.962–198.491)	(45.464–208.787)	(23.661–224.823)	(52.123–197.644)	(49.324–199.353)	(51.374–189.655)	(30.876–204.96)	(38.628–186.572)
MPV	10.020	F	10.066	10.074	0.092	10.088	10.098	10.015	10.013	10.011
	(8.471–11.570)		(8.541–11.590)	(8.742–11.407)	(8.537–11.647)	(8.537–11.639)	(8.565–11.631)	(8.528–11.503)	(8.489–11.537)	(8.562–11.460)
		M	9.975	9.983	9.989	9.966	9.965	9.975	10.040	9.967
			(8.407–11.542)	(8.659–11.307)	(8.400–11.577)	(8.415–11.517)	(8.398–11.532)	(8.407–11.542)	(8.386–11.693)	(8.518–11.417)

Unit: MPV, fL.
LMR = lymphocyte-monocyte ratio, MPV = mean platelet volume, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, SD = standard deviation.

the reference values as the mean ± 1.96 standard deviation. Our analysis showed that the mean NLR across all ages was 1.65 (0.79), and the values for men and women were 1.63 (0.76) and 1.66 (0.82), respectively. The mean LMR, PLR, and MPV were 5.31 (1.68), 132.40 (43.68), and 10.02 (0.79), respectively. These data demonstrate that all markers differed significantly between men and women ($P < .05$). Except for the NLR, the values were higher in women than in men. Figure 1 shows the trends and changes of each marker with age and sex.

4. Discussion

The present study provides the first report of reference values for NLR, LMR, PLR, and MPV according to sex and age of more than 10,000 patients from a single racial group. A few studies have been published showing the reference or normal values for these factors; however, these studies were conducted using from a small cohort of patients with different races. To the best of our knowledge, this is the first study to compare multiple markers such as NLR, LMR, PLR, and MPV by age or sex from a large, healthy population of a single race.

The NLR has been described as a predictor of mortality in patients with acute coronary syndrome and many different types of cancer. This marker has also been reported to predict the prognosis of critically ill patients in intensive care.[1–6] Generally, a higher NLR is correlated with high mortality and poor prognosis. Many retrospective, prospective studies have suggested "high risk" cutoff levels of pretreatment NLR from Kaplan-Meier curves and multivariate Cox-regression analysis. These studies often, however, do not consider the disease category, age, and race of patients, which are important attributes for applying this data to clinical situations. For example, the NLR cutoff values for prognosis from different studies varies from 2.5 to 5, and studies from western countries suggest a higher cutoff value than Asian or African ones.[10–13] A study of the average value and racial difference in the United States reported that the NLR was higher than 2 in all races except non-Hispanic black patients.[14] The results of our study showed that the NLR in the Asian population was generally lower than other races, which is consistent with previous studies. The mean NLR across all ages in men and women was 1.63 (0.76) and 1.66 (0.82), respectively.

The NLR was also different between sexes at the same age (Fig. 1A). Several studies have showed that hematopoiesis changes at different estrogen levels during menopause.[15] Sex hormones, which are represented by estrogen and progesterone, increase neutrophil recruitment from the bone marrow, as well as delay apoptosis. Thus, it was not surprising to observe a significant decrease in neutrophil count in women older than 40 years in our study. A decrease in neutrophil count in menopause women with relatively unchanged lymphocyte count results in a decrease in NLR. Consequently, the NLR in women is higher in age groups of <50 years than men, whereas in age groups of >51 years, it is the reverse.

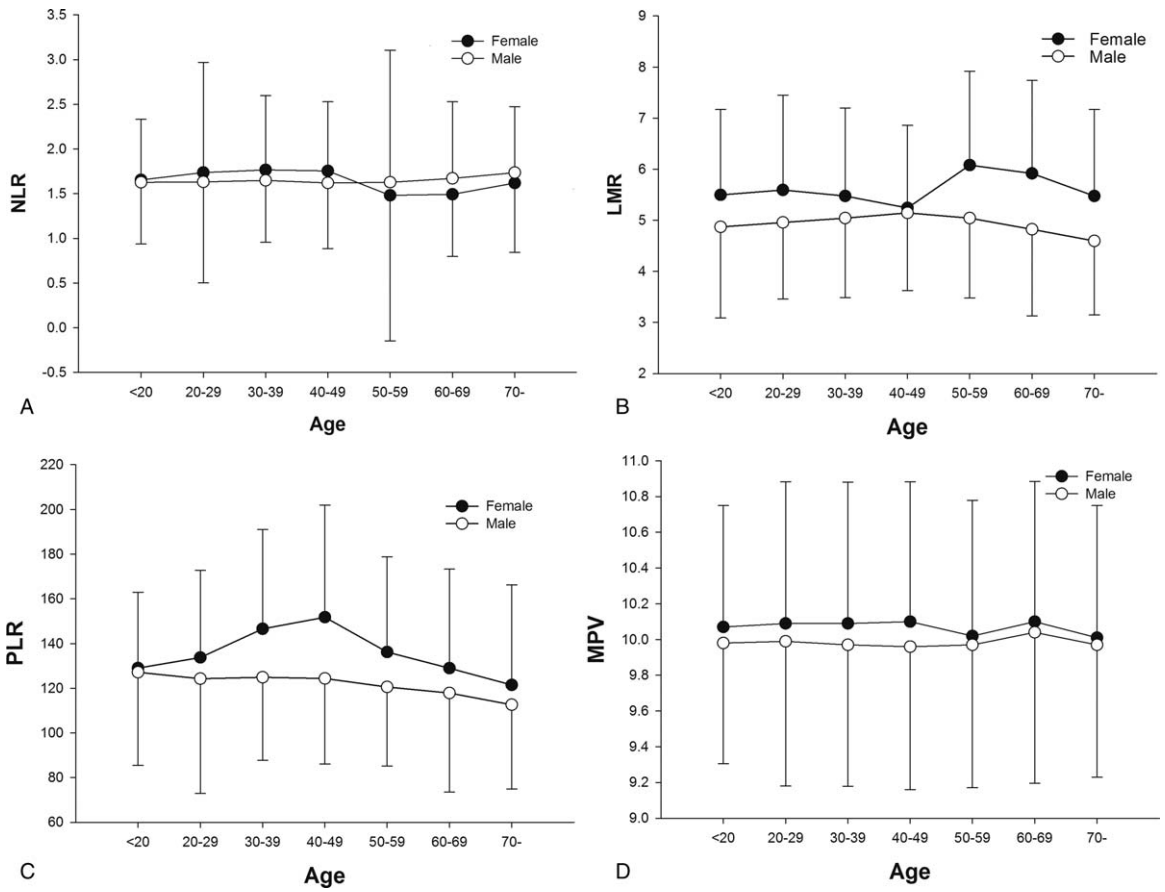

Figure 1. NLR (A), LMR (B), PLR (C), and MPV (D) in men and women in different age groups. LMR = lymphocyte-monocyte ratio, MPV = mean platelet volume, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio. Data shown are mean (standard deviations) of mean in men and women, respectively, in each age group.

Although NLR is the most representative marker under investigation, many studies have focused on other baseline hematological markers which suggest a systemic inflammatory response. Tumor-associated monocytes, another main regulator of cancer inflammation, also play a major role in the systemic inflammation response to tumors. Thus, LMR has been suggested to be an important factor for predicting prognosis in patients with hematologic malignancies and tumors, such as lung cancer or colon cancer.[16,17]

In this study, the mean LMR was 5.31 (1.68). The effects of menopause on hematopoiesis were also seen in the LMR (Fig. 1B). This baseline for this marker is also thought to vary according to race, age, and sex; however, normal or reference values from a healthy population have yet to be reported. In previous studies, patients with preoperative LMR under 2.57 or 2.83 were considered a "high risk" group with various solid tumors and lymphomas.[17,18] These cutoff values are included in the reference value of LMR in this study. In order to apply LMR cutoff values based on a normal healthy population, further studies of baseline differences by race, age, and sex should be performed.

Platelets secrete and express a large number of substances that are important mediators of coagulation, thrombosis, and inflammation. The platelet count and volume determined by hematopoiesis are affected by the systemic inflammatory state. MPV, as a determinant of platelet function, is a newly emerging risk factor for atherothrombosis and may become a potentially useful prognostic biomarker in cardiovascular patients. PLR based on platelet count variation was also studied as a prognostic inflammatory marker associated with multiple cancers. There have yet to be any studies showing the reference values of MPV and PLR. Our study demonstrates that the mean reference value for PLR and MPV are 132.40 (46.794–218.006) and 10.020 (8.471–11.570), respectively. These results may provide preliminary data for further studies.

This study was conducted to establish the preliminary reference values of NLR, LMR, PLR, and MPV in a healthy general public. To approximate the normal values of NLR and other markers of healthy cohort, we used the data from health check-up in tertiary hospital and excluded patients with any medical history and current medications. Considering the drinking and smoking cessation for health check-up for 3 to 7 days, it is thought to be the maximum effort to ensure the consistency of the physical status of the patients.

The present study had some limitations. First, NLR, LMR, PMR, and MPV are known to be associated with the inflammatory response. Thus, we excluded patients with any medical history because of the potential for anti-inflammatory effects stemming from some medications. We also excluded data from patients with any cancer history because of the possibilities of chemotherapy or radiation therapy. As a result, our data may underestimate the degree of systemic inflammation in the healthy, disease-free population. Second, we did not control the process and timing of blood collection and analysis. Depending on the length of time between blood collection and analysis, the composition of blood cells could be altered or destroyed. In particular, platelets can swell over time and cause inaccurate MPV results.

This study provides preliminary reference data on NLR, LMR, PMR, and MPV from different age and sex groups in South Korea. The data suggest that different cutoff values should be set according to race and age. Despite being inexpensive and easy, the application of hematologic markers in clinical practice can be challenging because of a lack of standardization and evidence. In order to determine the level or cutoff at which disease progression can be predicted, the evaluation of normal or reference values is required. Therefore, this study may be helpful for the establishment of thresholds which predict disease progression in various clinical practices.

Author contributions

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