Relationship of the neutrophil/lymphocyte ratio with cardiovascular risk markers in premenopausal and postmenopausal women

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Abstract

Introduction: Cardiovascular disease is more frequent in postmenopausal women. Atherosclerosis is associated with inflammation and the neutrophil/lymphocyte ratio (NLR) is a marker of inflammation whose behavior in postmenopause is unknown.

Aim of the study: To know the relationship of the NLR with cardiovascular risk markers in premenopausal and postmenopausal women.

Material and methods: Premenopausal and postmenopausal women were studied, in all of them a complete hemogram and the NLR, platelet/lymphocyte ratio (PLR) were calculated, also glucose and lipids levels were measured. In all of them subcutaneous and visceral fat, carotid intima-media thickness (IMT), epicardial fat were measured by ultrasound Also baseline and after flow-mediated stimulus the arterial diameter, the pulsatility index and the resistive index of the brachial artery were measured by ultrasound. The results are reported with medians and intervals, Mann-Whitney U and Spearman correlation analysis were performed.

Results: Eighty two patients were recruited, 41 premenopausal and 41 postmenopausal. When comparing both groups there was no difference in glucose, lipids, NLR, PLR, carotid IMT, epicardial fat, subcutaneous fat, visceral fat or Doppler parameters of the brachial artery.

Conclusion: NLR was not different between premenopausal and postmenopausal women but abnormal PLR was greater in those postmenopausal with vasomotor symptoms.

Key words: neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, inflammation, premenopause, postmenopause.

Introduction

The climacteric is the stage in the life of the woman that precedes and follows the cessation of menstruation (menopause), initially due to the decrease and subsequently to the cessation of estrogen and progesterone production by the ovary [1]. It is known that cardiovascular disease (CVD) is more frequent in older women than in men of the same age [2], and is an important cause of mortality in women. A woman living in the western world has a 46% risk of suffering from atherosclerotic coronary disease in the rest of her life and a 31% risk of dying from coronary heart disease [3, 4]. The symptoms of climacteric can be controlled with the use of hormone therapy whether with estrogen or estrogen plus progestogen, although this has not been recommended for the prevention of CVD [5]. However, it has been observed that estradiol has anti-inflammatory properties in vitro [6] and the use of hormone therapy (HT) in the first 10 years after menopause is not associated with cardiovascular risk as it is when administered after that period of time [7]. Lipid changes and endothelial damage are involved in the genesis or atherosclerosis which is a chronic inflammatory process, due to the inability of the organism to stop an acute inflammatory process [8]. In postmenopause it has been observed that the tumor necrosis factor (TNF) alpha rises, probably in relation to the decrease in estrogen and progesterone, which favors insulin resistance and the modification in fat distribution [9]. The neutrophil/lymphocyte ratio (NLR) is an inflammatory state marker that predicts cardiovascular [10] and renal complications in patients with diabetes [11], as well as mortality due to cardiovascular causes in patients on hemodialysis [12] and in patients with difficult to control hypertension [13]. Likewise, the NLR has been considered as a marker of systemic dysfunction in asymptomatic subjects [14]. The endothelium...
acts as a barrier and facilitates various processes, due to the expression of various molecules, including nitric oxide (NO) which is produced from L-arginine by NO synthetase and which is activated by various stimuli such as hypoxia, serotonin and increased vascular flow. High lipid levels and insulin resistance have a harmful effect on the endothelium, which is manifested among others by the loss of the endothelial NO activity and may precede CVD for several years [15, 16].

Obesity is closely related to CVD [17], and its prevalence is twice as high in postmenopausal women as in premenopausal women [18]. Obesity has been associated with higher fasting glucose levels, interleukin 6, C-reactive protein, being these last two markers of inflammation, correlating the latter with the number of leukocytes, in addition to the fact that the platelet count is higher in obese [19]. The increase in visceral fat is associated with high levels of triglycerides and low levels of high density cholesterol (HDL-C) [20] as well as with alterations in insulin sensitivity [21], which is an important component of the metabolic syndrome. Some authors have suggested that the detection of visceral fat allows the identification of those patients with high-risk metabolic syndrome [22] since it is associated with inflammation and release of pro-inflammatory cytokines [23]. In the menopausal transition adiponectin decreases and visceral fat is increased which has been associated with insulin resistance and decreased HDL-C.

Abdominal fat can be measured with different methodologies including abdominal ultrasound. In one study it was found that visceral fat correlated positively with systolic blood pressure in the group with carotid intima media thickness (IMT) > 1 mm and which is known to be an indicator of cardiovascular risk [24].

Atherosclerosis is a systemic disease that is responsible for many of the cardiovascular and cerebrovascular events, which are directly related to the increase in IMT in different blood vessels [25]. The carotid artery IMT has been the most studied marker and has been validated by official medical organizations. It has been reported that a 0.1 mm increases in IMT are associated with a 10% to 15% increase in the risk of having a myocardial infarction and from 13% to 18% to have a cerebrovascular event [26].

For endothelial function evaluation there are several non-invasive techniques, one of them is the Doppler ultrasound [27]. The flow-mediated dilation (FMD) in the peripheral arteries after the chemical and/or physical stimulation consist in the regulation in vascular tone and blood flow, which corresponds to that of the coronary arteries and a correlation between coronary abnormalities [28] and brachial artery flow has been reported [29]. Also, subcutaneous fat correlates inversely with FMD that is an indirect marker of the endothelial health status [30].

Recently the measurement of epicardial fat has been used as an indicator of cardiovascular risk and has been correlated with other markers of endothelial dysfunction. This is closely related to visceral fat [31], the metabolic syndrome [32] and is also increased in oophorectomized women [32].

Cardiovascular disease is one of the main causes of death so finding a marker that can be easily applied to a big group of people will be useful to early detect people at risk.

Therefore, the objective of this study was to determine the relationship of the NLR with different markers of cardiovascular risk between pre- and postmenopausal women.

**Material and methods**

Premenopausal and postmenopausal women who attended the outpatient endocrine gynecology clinic were studied. All were consecutively as they arrived and accepted to participate. In all of them, age (years), associated diseases, concomitant medications, age at the time of menopause (years) were documented. Use of HT, time of use of HT (months), type of HT, age at the beginning of TH (years), Weight (kg), height (meters) were measured and body mass index (weight/height²) was calculated. Likewise, the waist perimeter (cm), the hip perimeter (cm) were measured and the waist-hip ratio

| Characteristics          | Premenopausal \(n = 41\) | Postmenopausal \(n = 41\) | \(p\) |
|--------------------------|--------------------------|--------------------------|------|
| **Age (years)**          | 49 (42-55)               | 54 (42-86)               | 0.000|
| **How many hot flushes a day** | 3 (1-11)       | 4 (1-20)                | 0.06 |
| **Body mass index**      | 27.7 (22-42.9)          | 27.1 (19.8-37.8)        | ns   |
| **Waist hip index**      | 0.89 (0.71-0.97)        | 0.9 (0.77-0.98)         | ns   |
| **Glucose (mg/dl)**      | 95.0 (73.0-127.0)       | 91 (72-107)             | ns   |
| **Cholesterol (mg/dl)**  | 203.5 (141-254)         | 196 (105-319)           | ns   |
| **Triglycerides (mg/dl)**| 149.5 (49-316)          | 144 (60-315)            | ns   |
| **HDL-C (mg/dl)**        | 50 (38-99)              | 45.5 (30-99)            | ns   |

HDL-C – high density cholesterol
(WHR, waist perimeter/hip perimeter) was calculated. Blood pressure (mm Hg), glucose (mg/dl), cholesterol (mg/dl), triglycerides (mg/dl), HDL-C (mg/dl) were measured, and a complete hemogram was done.

The NLR was calculated by dividing the total number of neutrophils by the total number of lymphocytes being normal when \( \leq 4 \), also the platelet/lymphocyte ratio (PLR) was calculated by dividing the total number of platelets by the total number of lymphocytes being normal when \( \leq 0.54 \) [35].

For the study a Voluson 730 Pro device (General Electric Healthcare, Austria GM GH) was used. All patients underwent abdominal ultrasound with a 5 MHz transducer to measure subcutaneous fat and visceral (intrabdominal) fat. For this the transducer was placed in the midline, 1 cm below the navel and subcutaneous fat was considered as the distance between the skin and the external face of the rectus abdominis muscle (cm) and the visceral fat was considered as the distance from the internal face of the rectus abdominis muscle and the anterior wall of the aorta (cm) [34]. The visceral fat/subcutaneous fat ratio was calculated, being normal when \( \leq 0.54 \) [35].

The carotid IMT was then measured with a 7.5 MHz transducer, in the soft tissue category, locating the carotid artery 1 cm from its bifurcation, the image was visualized on the screen and measured the distance between the first and the second echogenic line. The highest given value was used for the analysis and was considered normal when \( \leq 1 \) mm [24].

For epicardial fat measurement a mode M ultrasound was done with a 3.5 MHz transducer considering the hypoechoic space between the outer wall of the myocardium and the visceral layer of the pericardium in the parasternal longitudinal view and perpendicular to the free wall of the right ventricle perpendicular to the aortic ring at the end of systole in three cardiac cycles [36]. It was considered abnormal when \( \geq 5 \) mm [37-40].

Finally all of them underwent Doppler ultrasound of the brachial artery with a 7.5 MHz transducer. For this, the transducer was placed perpendicularly in the distal third of the brachial artery and the internal diameter was measured (mm), when the double line pattern was clearly seen, the pulsatility index (PI) was calculated: maximum systolic velocity minus minimum diastolic velocity divided by the average velocity during the entire cycle and the resistive index (RI): maximum systolic velocity minus final diastolic velocity divided by the maximum systolic speed The hyperemic stimulus was induced by placing the sphygmomanometer cuff on the right arm and insufflating it up to 50 mm Hg above the maximum systolic pressure for five minutes. Subsequently, the cuff was deflated and removed, 60 seconds later the arterial diameter, the PI and the RI were measured again [41, 42].

### Statistical analysis

The results are reported with medians and intervals. The comparison between both groups was carried out by Mann-Whitney U test. Spearman’s correlation analysis of the NLR and the PLR was performed with the subcutaneous fat thickness, visceral fat thickness, IMT, epicardial fat, in addition the baseline arterial diameter, PI and RI were measured at baseline and after the hyperemic stimulus values. For the calculations, the SPSS program for Windows V20 was used. A statistically significant difference was considered when the value of \( p \) was \(< 0.05\).

The sample size was calculated with the Medcalc V 18.5 program, considering an \( \alpha \) error 0.05 and a \( \beta \) error of 0.1 with a difference between the means of 0.6 and a standard deviation in group 1 of 0.52 and in group 2 of 1.18. A relationship between group 1 and two of 1/1 with a standard deviation in group 1 of 0.52 and in group 2 of 1.18 was considered leaving 38 in the premenopausal group and 38 in the postmenopausal group.

The protocol was authorized by the Ethics in Research Committee and by the Local Research in Health Committee of the UMAE Hospital de Gineco Obstetricia

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**Table 2. General data in pre- and postmenopausal women divided by the presence or absence of vasomotor symptoms (VMS)**

| Characteristics | Pre without VMS \((n = 10)\) | Pre with VMS \((n = 31)\) | *p* | Pos without VMS \((n = 13)\) | Pos with VMS \((n = 28)\) | *p* |
|-----------------|-----------------------------|-----------------------------|-----|-----------------------------|-----------------------------|-----|
| Age (years)     | 47 (42-55)                  | 49 (44-54)                  | ns  | 56 (48-86)                  | 52.5 (42-63)                 | 0.004 |
| Time since menopause (months) | 0 (0-0)                  | 0b ns                      | 96 (12-588) c | 24 (12-300) d | ns |
| How many hot flushes a day | 0.89 (0.71-0.94) | 0.88 (0.77-0.97) | ns | 0.88 (0.86-0.98) | 0.91 (0.77-0.97) | ns |
| BMI             | 197.5 (141-237)             | 204 (141-254)               | ns  | 202 (141-319)               | 194 (105-315)               | ns  |
| WHR             | 51 (41-73)                  | 48 (38-99)                  | ns  | 46 (38-81)                  | 45 (30-99)                  | ns  |

BMI = body mass index, WHR = waist-hip ratio, *p* \(< 0.004, **p* \(< 0.005
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“Luis Castelazo Ayala” from the Social Security Mexican Institute at Mexico City, with the number R-2018-3606-031, and all patients signed the informed consent form.

The funding of the project was with resources of the hospital and the researchers.

Results

There were included 82 patients, 41 premenopausal (group 1) and 41 postmenopausal (group 2). The age in group 1 was 49 (42-55) years and in group 2 55 (42-86) years. Time since menopause was in group 2 49 (12-588) months. When comparing the premenopausal group with the postmenopausal group as BMI, WHR, glucose, cholesterol, triglycerides and HDL there were no differences between the two groups (Table 1).

When comparing those premenopausal women with and without vasomotor symptoms (VMS), there was no difference in any of the analyzed parameters, while in postmenopausal patients the age was greater in those without VMS (p < 0.000) as well as the time since menopause (p < 0.005) in the other analyzed parameters there were no significant differences (Table 2).

When comparing premenopausal women with postmenopausal women both with hot flashes, the age was greater in postmenopausal patients, as was the number of VMS. In the group without hot flashes there was no difference in any of the analyzed parameters (Table 2).

When comparing the NLR and the PLR between premenopausal and postmenopausal women, no significant differences were found. Also IMT, epicardial fat, subcutaneous fat, visceral fat, visceral fat index/subcutaneous fat did not differ between groups.

In the analysis of the brachial artery Doppler parameters, the arterial diameter, the PI, the RI at baseline and after the hyperemic stimulus, didn’t show significant differences. The same happened when analyzing the differences between baseline and final values of the arterial diameter, PI and RI (Table 3) In those with vasomotor symptoms the proportion of women with normal PLR was greater in those premenopausal when compared with those postmenopausal 60.9% vs 39.1%, p < 0.017.

When comparing premenopausal women with and without VMS there were no differences in the analyzed parameters and the same happened when comparing premenopausal women with postmenopausal women with and without VMS. Only the number of neutrophils were sig-
significantly more numerous in the premenopausal group with VMS 3.6 (2.4-5.6) than in the premenopausal group without VMS 2.9 (2.0-4.3), \( p < 0.042 \).

In premenopausal and postmenopausal women no differences were found between the analyzed parameters after dividing according to BMI. After dividing to WHR in premenopausal women statistical significant difference was found in the difference between final and baseline brachial artery diameter 0.08 (−0.08-0.13) vs −1.75 (−0.14) \( p < 0.052 \).

In premenopausal group there was a correlation between the NLR and the cholesterol level 0.303, \( p < 0.057 \), and with the triglycerides 0.376, \( p < 0.017 \). Also there was among the PLR with the baseline arterial diameter 0.352, \( p < 0.024 \), with the baseline IR 0.315, \( p < 0.045 \) and with post-hyperemic stimulus RI 0.394, \( p < 0.11 \).

In the postmenopausal group there was between NLR and baseline RI 0.336, \( p < 0.032 \) between NLR and the difference between final and baseline RI −0.371, \( p < 0.017 \). Between the PLR and the number of hot flashes per day −0.456 \( p < 0.015 \), with the baseline PI 0.417, \( p < 0.007 \), with the baseline IR, \( p < 0.007 \), with the difference between the final and baseline PI −0.345, \( p < 0.027 \) and with the difference between the final and baseline RI −0.472, \( p < 0.002 \) (Tables 4 and 5).

### Discussion

Inflammation has been involved in various processes including atherosclerosis. After menopause an

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### Table 4. Correlation analysis between the neutrophil lymphocyte ratio and the platelet lymphocyte ratio with vasomotor symptoms and laboratory variables

| Variable               | Premenopausal (n = 41) | Postmenopausal (n = 41) |
|------------------------|------------------------|-------------------------|
| NLR                    | p                      | PLR                     | NLR                    | p                      | PLR                     |
| How many VMS a day     | −0.022                 | 0.910                   | 0.108                  | 0.569                  | −0.250                  | 0.200                   | −0.456                 | 0.015                  |
| Cholesterol (mg/dl)    | 0.303                  | 0.057                   | 0.168                  | 0.299                  | 0.046                   | 0.777                   | 0.273                  | 0.084                  |
| Triglycerides (mg/dl)  | 0.376*                 | 0.017                   | 0.075                  | 0.646                  | 0.105                   | 0.513                   | 0.090                  | 0.576                  |

Results represent Sperman’s correlation coefficient and \( p \) values. VMS – vasomotor symptoms, NLR – neutrophil/lymphocyte index, PLR – platelet/lymphocyte ratio

### Table 5. Correlation analysis between the neutrophil/lymphocyte ratio, the platelet/lymphocyte ratio and Doppler parameters of brachial artery in pre- and postmenopausal women

| Variable                                         | Premenopausal | Postmenopausal |
|--------------------------------------------------|---------------|---------------|
|                                                  | NLR p         | PLR p         | NLR p         | PLR p         |
| Baseline artery diameter                         | 0.276         | 0.080         | 0.352         | 0.024         | −0.236        | 0.137        | −0.089        | 0.581                  |
| Baseline pulse rate                               | 0.057         | 0.817         | 0.273         | 0.084         | 0.155        | 0.333        | 0.417        | 0.007                  |
| Baseline resistance index                         | 0.061         | 0.703         | 0.315         | 0.045         | 0.336        | 0.032        | 0.417        | 0.007                  |
| Baseline resistance index post hyperemic stimulus | 0.017         | 0.917         | 0.394         | 0.011         | 0.123        | 0.442        | 0.100        | 0.532                  |
| Final arterial diameter minus baseline arterial diameter | −0.182        | 0.254        | −0.054        | 0.738         | 0.223        | 0.161        | 0.295        | 0.061                  |
| Final pulsatility index minus baseline pulsatility index | −0.073        | 0.651         | −0.102        | 0.525         | −0.206       | 0.196        | −0.345       | 0.027                  |
| Final resistance index minus baseline resistance index | −0.020        | 0.901         | 0.145         | 0.366         | −0.371       | 0.017        | −0.472       | 0.002                  |

Results represent Sperman’s correlation coefficient and \( p \) values. NLR – neutrophil/lymphocyte index, PLR – platelet/lymphocyte ratio
### Table 7. Correlation analysis between the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and intima-media thickness, subcutaneous fat/viscera fat ratio and brachial artery Doppler parameters in pre- and postmenopausal women, further divided by the presence or absence of vasomotor symptoms

| Parameter                         | NLR  | p     | PLR  | p     | NLR  | p     | PLR  | p     | NLR  | p     | PLR  | p     | NLR  | p     | PLR  | p     |
|-----------------------------------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|
|                                  | VMS no | VMS no | VMS no | VMS no | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes |
|                                  | n = 10 | n = 13 | n = 13 | n = 13 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 |
| Intima-media thickness           | 0.164 | 0.651 | 0.697* | 0.025 | −0.071 | 0.817 | 0.071 | 0.817 | 0.011 | 0.954 | −0.131 | 0.481 | 0.045 | 0.821 | 0.009 | 0.964 |
| Cholesterol                      | 0.745* | 0.013 | 0.297 | 0.405 | 0.231 | 0.448 | 0.599* | 0.031 | 0.203 | 0.282 | 0.117 | 0.538 | −0.007 | 0.971 | 0.220 | 0.260 |

Results represent Spearman’s correlation coefficient and p values. VMS – vasomotor symptoms, NLR – neutrophil/lymphocyte index, PLR – platelet/lymphocyte ratio

### Table 6. Correlation analysis between the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio with anthropometric and laboratory parameters in pre- and postmenopausal women, further divided by the presence or absence of vasomotor symptoms

| Parameter                         | NLR  | p     | PLR  | p     | NLR  | p     | PLR  | p     | NLR  | p     | PLR  | p     | NLR  | p     | PLR  | p     |
|-----------------------------------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|
|                                  | VMS no | VMS no | VMS no | VMS no | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes | VMS yes |
|                                  | n = 10 | n = 13 | n = 13 | n = 13 | n = 13 | n = 31 | n = 13 | n = 13 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 | n = 28 | n = 31 |
| Body mass index                  | 0.164 | 0.651 | 0.697* | 0.025 | −0.071 | 0.817 | 0.071 | 0.817 | 0.011 | 0.954 | −0.131 | 0.481 | 0.045 | 0.821 | 0.009 | 0.964 |
| Cholesterol                      | 0.745* | 0.013 | 0.297 | 0.405 | 0.231 | 0.448 | 0.599* | 0.031 | 0.203 | 0.282 | 0.117 | 0.538 | −0.007 | 0.971 | 0.220 | 0.260 |

Results represent Spearman’s correlation coefficient and p values. VMS – vasomotor symptoms, NLR – neutrophil/lymphocyte index, PLR – platelet/lymphocyte ratio

SF – subcutaneous fat, VF – visceral fat
increase in cardiovascular events is more frequent [3, 4], most likely due to a decrease in estradiol concentrations that have an anti-inflammatory effect [6].

The NLR, a marker of inflammation, has allowed the prediction of cardiovascular complications [10]. That is why in this study it was intended to observe if there was any difference in this ratio between pre- and postmenopausal women and to determine its relationship with other cardiovascular risk markers such as fat visceral, epicardial fat and endothelial function, however this study found no differences in NLR and PLR between pre- and postmenopausal women, nor after having been divided based on the presence or not of vasomotor symptoms.

In premenopausal women, the positive correlation between the NLR with cholesterol and triglycerides may indicate an increased risk of atherosclerosis as it is an inflammatory process [43].

The correlation of the PLR with the baseline AD, with baseline RI and with post-hyperemic stimulus RI indicates the relation of inflammation with these parameters.

In the postmenopausal patients there was a positive correlation of the NLR with the baseline RI and negative with the difference between final and baseline hyperemic stimulus RI, for which we have no explanation. There was a negative correlation between the PLR and the number of VMS per day, positive with the baseline PI, with the baseline RI, with the difference between final and baseline AD and the negative DAB, as well as with the difference between final and baseline PI final PI and the baseline PI, with the baseline RI, with the difference between final and baseline RI. In the first case, having less VMS, less inflammation is associated with lower cardiovascular risk, as has already been reported [44, 45].

In premenopausal women without hot flashes, the NLR correlated positively with cholesterol and the PLR positively correlated with the BMI.

In the postmenopausal group without hot flashes, the PLR correlated positively with cholesterol, with a greater cardiovascular risk associated with inflammation and dyslipidemia [43].

In the premenopausal group with hot flashes, the NLR positively correlated with the WHR, which implies that upper level fat distribution is associated with greater inflammation and greater cardiovascular risk [20].

In postmenopausal women with hot flashes, the PLR positively correlated with HDL-C levels for which we have no explanation.

In the premenopausal group without VMS, there was a correlation between PLR and RI and with post hyperemic stimulus RI this means that hot flashes influence inflammation, and vascular resistance [45].

In the premenopausal group without VMS, there was a negative correlation of the NLR with the SF/VF ratio, which means that the inflammation is lower to greater parietal fat [20, 23, 35, 46]. Although other studies have found a greater inflammatory effect of parietal fat [47].

In the group of premenopausal patients with VMS, there was a positive correlation between the PLR and baseline arterial diameter, which indicates that women with hot flashes have greater inflammation that affects the vascular endothelium [9, 40-42, 48, 49].

In the postmenopausal group there was a negative correlation between the PLR and the IMT, which shows a greater risk of atherosclerosis with lower inflammation for which we have no explanation.

The limitation of this study was sample size since after division of the main group in subgroups no statistical differences were found, so it is needed a greater sample size to really determine if it can be used as a clinical aid. So it is possible to conclude that inflammation is related with other cardiovascular risk markers, NLR was not different between premenopausal and postmenopausal women but abnormal PLR was greater in those postmenopausal with vasomotor symptoms.

Disclosure
The authors report no conflict of interest.

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