

Inflammatory Biomarkers: The Hidden Triggers of Hot Flashes in Menopause

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Abstract

Menopausal hot flashes (HFs) may potentially elevate inflammatory biomarkers (IB). Neutrophil-to-Lymphocyte Ratio (NLR) and Lymphocyte-to-Monocyte Ratio (LMR) are gaining attention as accessible and cost-effective measures of IB. This study explores the association between these biomarkers and HFs in menopause. This cross-sectional study included healthy menopausal women aged 40-60 in groups without HFs (n=40) and with HFs (n=120) using consecutive sampling. The women experiencing HFs recorded HFs number on a card over two weeks. We reckoned the HFs severity using the modified Kupperman index. We measured the Complete Blood Count and computed NLR and LMR. We conducted multiple and ordinal logistic regression analyses. The median of NLR and LMR had no significant difference between the two groups. There were significant discrepancies in NLR among HFs severity-based groups, contrary to LMR. NLR had an elevating impact on HFs severity as determined by ordinal logistic regression (Odds Ratio=2.180, 95% CI: 1.270-3.744). Our research indicated that cumulative changes in NLR may be connected to the HFs severity. Concerning the possible association between HFs and endothelial dysfunction, adjusting NLR in perimenopause seems to control HFs and their probable consequences. It is reasonable to conduct longitudinal studies to clarify the causal relationship between inflammation and HFs.

Key Words: “Hot Flashes”, “Lymphocytes”, “Menopause”, “Monocytes”, “Neutrophils”

Respected Assessor

The briefly submitted paper is a small part of our study, approved by Guilan University of Medical Sciences, which has been fully published in PLOS ONE journal. This part of the article has been sent to be presented in that congress. Therefore, it should be noted that we only need to publish the abstract of this paper at that conference. Our article cited is as follows:

Didevar N, Rezasoltani P, Pourgholaminejad A, Kazemnezhad Leyli E, Seyednoori T, Zahiri Sorouri Z. Interleukin-17, C-reactive protein, Neutrophil-to-Lymphocyte ratio, Lymphocyte-to-Monocyte ratio, and lipid profiles in healthy menopausal women with or without hot flashes: A cross-sectional study. PLoS One. 2023 Nov 22;18(11):e0291804. doi: 10.1371/journal.pone.0291804. PMID: 37992065; PMCID: PMC10664956.

Sincerely,

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Introduction

Menopause, characterized by declining endogenous estrogen levels, can emerge hot flashes (HFs) and may potentially elevate systemic inflammatory markers (SIMs) (1, 2). The interaction between SIMs and HFs is crucial in understanding the development of endothelial dysfunction, hypertension, diabetes, and cardiovascular disorders (CVD) through menopause, ultimately raising healthcare expenditures (3). Notably, the Neutrophil-to-Lymphocyte Ratio (NLR) and Lymphocyte-to-Monocyte Ratio (LMR) are gaining attention as accessible and cost-effective measures of SIMs. Several studies suggested that peri/postmenopausal women exhibit changes in the ratios (4, 5). This study explores the association between these two biomarkers and HFs in healthy menopausal women, hypothesizing significant differences in the ratio levels between those with and without HFs.

Materials and Methods

In a cross-sectional study, we enlisted 160 healthy menopausal women aged 40-60. Regarding their HFs status, they were categorized into two groups by consecutive sampling: without HFs (n=40) and with HFs (n=120). We provided the women experiencing HFs during the three months before recruitment with a card and requested them to record the number of HFs they encountered over two weeks as part of a pilot study. We reckoned the HFs' severity in each study sample using

the modified Kupperman index, organizing the mean HFs into three severity levels: severity values of 1 (n=42), 2 (n=43), and 3 (n=35). Along with demographic/reproductive, clinical variables, and the HFs status, we measured Complete Blood Count (CBC) parameters, based on which we computed NLR and LMR for each group. We conducted multiple logistic regression analysis using the backward stepwise method to examine the association between the ratios and HFs in menopausal women, with and without HFs. Likewise, we performed ordinal logistic regression analysis to compare NLR and LMR in the HFs severity-based groups.

Results

We discovered no significant difference in the median of NLR and LMR between the two groups of menopausal women without and with HFs (Table 1). Similarly, there were no significant discrepancies in LMR among HFs severity-based groups. However, regarding NLR, there were significant differences among groups categorized by the severity of HFs (Table 2, 3 & Figure 1). As we observed, NLR had an elevating impact on HFs severity after adjusting for the confounding upshots of demographic and reproductive variables, as determined by ordinal logistic regression ($B=0.779$, $P=0.005$, Odds Ratio=2.180, 95% CI: 1.270-3.744) (Table 4).

Table1: Comparison of NLR and LMR in menopausal women without and with HFs

	Group		P
	Without HFs (n=40)	With HFs (n=120)	
NLR; Median (IQR)	1.45 (1.17-1.76)	1.47 (1.16-1.89)	0.610*
LMR; Median (IQR)	7.27 (5.79-9.13)	8.00 (6.00-11.42)	0.278*

NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; HFs, Hot Flashes; *Mann-Whitney u test

Table 2: Comparison of NLR and LMR in menopausal women in HFs severity-based groups

	Severity scale			P
	1	2	3	
NLR; Median (IQR)	1.25 (1-2)	1.57 (1-2)	1.71 (1-2)	0.013*
LMR; Median (IQR)	8.29 (6-12.25)	7.00 (6-10)	8.25 (6-10)	0.457*

NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; HFs, Hot Flashes; *Kruskal-Wallis test

Figure 1: Comparison of the median of NLR among the HF's severity-based groups

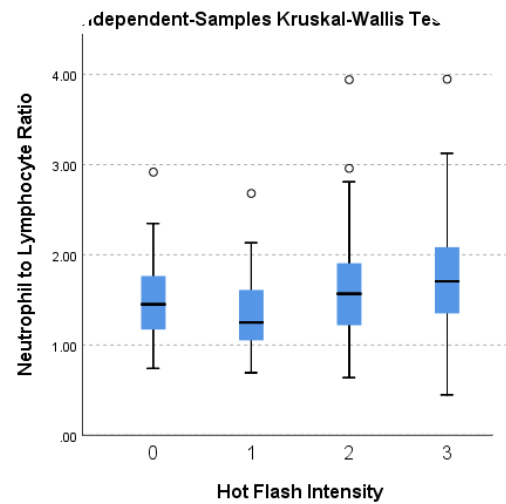


Table 3: The pairwise comparison of NLR in HF's severity-based groups

NLR					
Sample 1-Sample 2	Test statistic	Std. Error	Std. test statistic	Sig.	Adj. sig.*
0-1	14.072	10.235	1.375	0.169	1.000
1-2	-25.461	10.051	-2.533	0.011	0.068
1-3	-31.767	10.603	-2.996	0.003	0.016
0-2	-11.389	10.177	-1.119	0.263	1.000
0-3	-17.695	10.723	-1.650	0.099	0.593
2-3	-6.306	10.547	-0.598	0.550	1.000

NLR, Neutrophil-to-Lymphocyte Ratio; HF's, Hot Flashes; *Bonferroni test

Table 4: Results of the logistic regression (backward stepwise) and the ordinal regression comparing NLR and LMR between two groups without HFs and with HFs, and in HFs severity-based groups

Variables in equation		B	Std. Error	Sig.	Exp. (B)	95% C.I. for Exp. (B)	
						lower	upper
Step 1 ^a	NLR	0.556	0.397	0.162	1.743	0.801	3.795
	LMR	0.046	0.040	0.254	1.047	0.967	1.134
	Constant	1.673	3.532	0.636	5.330		
Severity ^a scale (1, 2, 3)	NLR	0.779	0.2759	0.005	2.180	1.270	3.744

NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; HFs, Hot Flashes; ^aMultiple logistic regression; ^aordinal logistic regression

Discussion

Chen et al. realized a drop in NLR after a decrease in neutrophil count and an increase in lymphocyte count in menopause. They ascribed this alteration to menopause-induced estradiol deficiency (4). Some studies noted a connection between declined estradiol and extended IL-17 levels in menopausal women (6, 7). Tahmasebinia et al. also reported raised IL-17 levels associated with increased neutrophil counts (8). As IL-17 enhanced, we expected neutrophil count and NLR to increase and estradiol to decrease. We found no significant association between NLR and HFs. However, we observed a tendency to expand IL-17 and increase the neutrophil count and NLR in menopausal women with HFs compared to those without HFs (9). Even though not significant, this finding was consistent with the pathophysiology of inflammation and dyslipidemia association with HFs (10). It contradicts Chen's data (dropped counts of neutrophils and NLR following decreased estradiol levels) (4).

We also observed that NLR significantly increased as the HFs severity extended. Adjustment for the covariates still retained this association. Lee et al. noted increased LMR in menopause and considered it would be associated with decreased estradiol levels (5). We observed women with HFs tended to expand LMR levels compared to those without HFs. However not statistically significant, this finding agreed with Lee's report and the pathophysiology of inflammation and

dyslipidemia association with HF (4, 10). We did not observe a significant association between the HF severity and LMR.

Conclusion

Our research indicated that cumulative changes in NLR, a systemic inflammatory marker, may be connected to the HF severity. This occasion may suggest HF as links between changes in SIMs and their outcomes. Concerning the possible association between HF and endothelial dysfunction, adjusting NLR in perimenopausal women seems to control HF and their probable consequences through menopause. Furthermore, it is reasonable to conduct longitudinal studies to clarify the causal relationship between inflammation and HF.

Acknowledgments

We appreciate the Vice Chancellor of Research and Technology of Guilan University of Medical Sciences (GUMS), Rasht, Iran, for approval of this research project (Ethics Code: IR.GUMS.REC.1399.636). We also value Hamzeh Yousefi Amin, the research laboratory supervisor, and his associates for their assistance and performance of the lab tests. Moreover, we would like to express our special thanks to all women who participated in this study.

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