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LYMPHOCYTE -TO- MONOCYTE AND PLATELET -TO-LYMPHOCYTE RATIOS AS SEX - DEPENDENT BIOMARKERS OF SUBCLINICAL INFLAMMATION IN PASSIVE SMOKERS

Huda Shareef Diab
Department of Science, Faculty of Basic Education-Al-Shirqat, Tikrit University, Salah Aldin, 34005, Iraq
huda.sh.diab@tu.edu.iq

Mohammed Mohsen Sharqat Ali Al-Jumaili
Salah Al-deen Education Directorate - Salah Al-deen Governorate, 34001, Ministry of Education, Iraq

Abstract. Passive smoking is often overlooked in clinical practice but does cause a long-lasting systemic inflammatory burden which can be detected by routine haematological indices which are low cost and inexpensive. The lymphocyte to monocyte ratio (LMR) and platelet to lymphocyte ratio (PLR) have been reported on in active smokers, but have not been studied in adult passive smokers, and not studied in sex specific stratification. The purpose of the present study was to compare LMR and PLR between passive smokers and healthy non smokers adults and to see the relationship between LMR and PLR with duration of passive exposure by dividing the samples based on sex. The current study is a cross sectional study that is comparative in nature and was conducted in Saladin Governorate, Iraq from February till May 2026. There were 28 Passive Smokers (18 male and 10 female) and 30 healthy controls (17 male and 13 female) over an age range of 25-45 years. Venous complete blood counts (CBC) were used to obtain both ratios. Data were analyzed statistically using SPSS version (26.0) and the Pearson correlation coefficient was used to determine the relationships between the exposure duration and the study indices, while independent samples t tests were used to determine the relationship between the duration of exposure and the study indices. The significance level was decided at $P \leq 0.05$. Aggregate level results - There was no significant difference between the LMR of passive smokers and controls (7.11 ± 0.60 vs. 7.12 ± 0.38, $P = 0.989$). Upon stratification, however, LMR was markedly lower in passively exposed females (5.17 ± 0.41 vs. 6.60 ± 0.51, $P = 0.030$), whereas it showed a non significant elevation in passively exposed males (8.19 ± 0.81 vs. 7.58 ± 0.54, $P = 0.237$). The overall passive smoking group had a significantly lower level of PLR (98.81 ± 6.14 vs. 110.27 ± 4.85, $P = 0.049$) but this was not significant in the sex specific sub-analyses. Of note, a negative correlation between LMR and duration of passive smoke exposure was found ($r = -0.27$, $P = 0.047$); this was not the case for PLR ($r = 0.06$, $P = 0.867$). There is a recognizable systemic inflammatory

signature in passive smoking that seems to differ in level of expression depending on the length of exposure to passive smoking and sex. Analysis by sex appears to be most sensitive in LMR, highlighting the importance of disaggregating data by sex. These results suggest that LMR and PLR could be useful early, inexpensive screening tools, but future, more definitive studies are needed to confirm this.

Keywords: Biomarkers; Complete Blood Count; Sex Factors; Systemic Inflammation; Tobacco Smoke Pollution

1. Introduction

Passive smoking is one of the world's largest preventable causes of death. Secondhand smoke (SHS) is estimated to kill more than 1.3 million people each year who have never smoked (World Health Organization, 2023). A global analysis of the 2021 Global Burden of Disease data found that age-standardised exposure rates for deaths were 38% among females and 30% among males in 204 countries, both of which have been on the rise since 2010 (Su *et al.*, 2025). The health burden of tobacco use is especially high in the Middle East, with a comprehensive GBD analysis of this region finding that 20.5% of all tobacco-attributable deaths are due to passive smoking, and disproportionately affecting younger age groups (Sultan *et al.*, 2024). The prevalence of active smoking among adults (aged 18 year and older) in a national STEPS survey carried out in 2015 in Iraq was 20.7%, which is inevitably accompanied by an parallel growth in involuntary exposure in the households and communities (Al Badri *et al.*, 2017). This is consistent with recent regional estimates on other countries bordering the region, where 67.3% of non smoking adults were estimated to be secondhand smokers, mostly in the home, and most often exposed by male family members (Madkhali *et al.*, 2023). Mechanistically, secondhand smoke components are known to induce systemic inflammatory pathways, as they can induce reactive oxygen species, activate nuclear factor κB and upregulate vascular adhesion molecules, all of which contribute to early atherogenesis and immune dysregulation (Saaoud *et al.*, 2023). Notably, the vascular effects of passive smoking are 80%-90% of the effects of active smoking (Barnoya & Glantz, 2005). This size of effect is further supported by a recent meta analysis of both active and passive smoking studies, which showed that there was a strong association between smoke exposure and changes in flow mediated dilation, an established early measure of endothelial integrity (Jia *et al.*, 2024). Also the damage is not limited to the cardiovascular system. Secondhand smoke exposure causes an estimated 6.94% of all deaths due to respiratory infection in children under 5 years of age (Xiang *et al.*, 2023). Passive smoking has also been associated with exacerbations of asthma and higher use of emergency health services (EHS) amongst paediatric populations (Wang *et al.*, 2015). Such exposure in adults increases the risk of chronic obstructive pulmonary disease by 2.25 times and the risk increases with the duration of exposure (Chen *et al.*, 2023). All these converging lines of evidence indicate that passive smoking triggers a wide range of systemic inflammation that extends beyond the lungs and should encourage the pursuit of blood markers that can be used routinely to monitor the silent inflammatory process. Complete blood count derived indices are a promising alternative to costly laboratory tests that are widely available and can be used to assess low grade systemic inflammation (Kösehasanoğulları *et al.*, 2025). Lymphocyte to monocyte ratio (LMR) is the ratio of adaptive immunity to innate immunity, and a decrease in LMR due to monocytosis has been associated with increased risk of chronic pulmonary disease and mortality in smokers (Sangani *et*

al., 2023). The platelet to lymphocyte ratio (PLR) reflects the interaction between haemostatic and immune system, in turn. Cekici *et al*. (2019) noted a significant negative correlation between LMR and smoking intensity, and Gumus *et al*. (2018) showed a significant decrease in PLR in smokers. However, the use of these indices for the case of passive smoking is still very limited in the literature. The assumption of a duration dependent relationship is well supported by recent evidence. Based on data from more than 182,000 participants from 22 research cohorts, Yao *et al*. (2025) found that the intensity of smoking showed a clear dose response relationship with subclinical inflammatory markers, suggesting that the dose response relationship should be similar between smoking and passive smoking as exposure increases. The immune response to smoking is not sexually monomorphic, that is, it is not unique to men and women. Oestrogen increases the efficacy of lymphocytes, while testosterone has the opposite effect on the activation of monocytes (Hoffmann *et al*., 2023). In addition, genomic evidence indicates a much wider immune modulation in female cells after being exposed to smoke—61 genes were affected versus 19 in males (Ashare & Wetherill, 2018). However, sex stratified studies exclusively on passive smoking are totally missing in literature of the Middle East, especially Iraq. Based on our literature search there is no investigation so far, that investigated LMR and PLR as separate diagnostic tools without stratification by sex and correlation with exposure duration. Past reports, including that of Cekici *et al*. (2019), have focused on individuals who are active smokers, or have included passive smokers in a "smoking" category without separate analysis. The aim of this study is to fill this integration gap. We aim to report the values of LMR and PLR in a sex-stratified sample of passive smokers, and to explore the association between LMR and PLR and duration of second hand smoke exposure. If they prove to be diagnostic, they are potential easy to access, low-cost markers for primary health care to detect occult systemic inflammation in communities at risk of passive smoking.

2. Materials and Methods

2.1. Study Design and Ethical Approval

The present study was a comparative cross sectional study that was carried out in Saladin Governorate, Iraq, from February to May 2026. The study was approved by the ethical committee of the institution (approval No. TU-BE-0005) and informed consent was obtained from all the participants after explaining the objective and methodology of the study in detail.

2.2. Participants and Exclusion Criteria

There were 58 participants, 28 (18 males, 10 females) were part of the passive smoking group and 30 (17 males, 13 females) were part of the healthy control group. Their ages were between 25 and 45 years. A convenience sampling method was used to recruit participants from among the companions of patients that attend outpatient consultation clinics.

Apparently healthy adults were included and active smokers (current or former), pregnant or lactating women, and people with chronic diseases (including cardiovascular disease, diabetes mellitus, chronic kidney or liver disease, and chronic inflammatory or autoimmune disease) were excluded to minimize potential confounding influences on the inflammatory parameters studied. The duration of passive smoke exposure (years) was estimated by asking each participant in the exposed group about the estimated number of years of exposure to tobacco smoke in the home or environment, and was recorded on a specific data collection

form. Notably, there was no biochemical objective evidence obtained (e.g., blood or urinary cotinine measurement).

2.3. Laboratory Assays

All participants had venous blood collected into EDTA containing tubes and analysed as whole blood with a Sysmex XP 30 haematology analyser (Sysmex Corporation, Japan). The two inflammatory ratios were then calculated using the following formulae:

- Absolute lymphocyte count ($\times 10^3/\mu L$) ÷ Absolute monocyte count ($\times 10^3/\mu L$) = Lymphocyte to monocyte ratio (LMR)
- The platelet to lymphocyte ratio (PLR) is the ratio of absolute platelet count ($\times 10^3/\mu L$) to absolute lymphocyte count ($\times 10^3/\mu L$).

2.4. Statistical Analysis

IBM SPSS Statistics for Windows 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Comparisons between the passive smoking and control groups—for the overall sample and then separately by sex—were carried out using independent samples t tests. Pearson's correlation coefficient was also calculated to evaluate the relationship between the passive smoke duration and study variables. Statistically significant differences (denoted with *) were regarded as those with a P value of ≤ 0.05.

3. Results

3.1. Sample Description and Baseline Characteristics

A total of 58 subjects were included in the study, consisting of 28 passive smoking (18 males and 10 females) and 30 healthy controls (17 males and 13 females). There were no significant differences between the two groups with respect to either age or BMI, thus confirming the homogeneity of the groups in these parameters, and reducing the possibility that either could affect the inflammatory indices being studied in the present study (Table 1).

Table 1. Comparison of baseline characteristics (age and body mass index) between the passive-smoking group and the control group

Parameters	Mean ± SD		*P*-Value
	SHS	Controls	
Age(year)	30.68±5.10	31.87±4.37	**0.344**
BMI (Kg/m^2)	27.96±4.38	28.87±4.83	**0.460**

SHS=Second-Hand Smoke; P-Value calculated using Independent samples t-test;
* Significant at P≤0.05

3.2. Comparison of Study Variable Means

At the aggregate level, no statistically significant difference was found between the passive smokers (7.11 ± 0.60) and the healthy controls (7.12 ± 0.38, P = 0.989) when looking at the lymphocyte to monocyte ratio (LMR) (Table 2; Figure 1). When analysed separately by sex, however, a distinct difference emerged. Passive smokers had a higher mean LMR (8.19 ± 0.81) than the healthy group (7.58 ± 0.54) but this difference was not statistically significant (P = 0.237) among males. The mean LMR for passively exposed females (5.17 ± 0.41) was in contrast significantly lower than for healthy females (6.60 ± 0.51), P = 0.030. With regard to platelet to lymphocyte ratio (PLR) (Table 2; Figure 1), passive smokers had a lower overall mean (98.81 ± 6.14) than controls (110.27 ± 4.85) and this difference was close to the conventional threshold of significance (P = 0.049). The pattern was the same on disaggregation by sex: the mean PLR for the

two sub-groups (passively exposed males, 91.50 ± 4.85 and healthy males, 97.20 ± 2.95) was directionally lowered but not statistically significant, while the mean PLR for passively exposed females (111.97 ± 14.39) and healthy females (125.22 ± 8.29) was likewise directionally lowered, though not statistically significant (P = 0.092).

Table 2. Comparison of the study variables between the passive smoking group and the control group—total sample, males, and females.

Parameters	SHS	Controls	*P*-Value	SHS	Controls	*P*-Value	SHS	Controls	*P*-Value
	Males and Females	Males and Females		Males	Males		Females	Females	
	Mean + SD	Mean + SD		Mean + SD	Mean + SD		Mean + SD	Mean + SD	
LMR	7.11±0.60	7.12±0.38	0.989	8.19±0.81	7.58±0.54	0.237	5.17±0.41	6.60±0.51	0.030*
PLR	98.81±6.14	110.27±4.85	0.049*	91.50±4.85	97.20±2.95	0.381	111.97±14.39	125.22±8.29	0.092

SHS=Second-Hand Smoke; *P*-Value calculated using Iindependent samples t-test; * Significant at *P*≤0.05

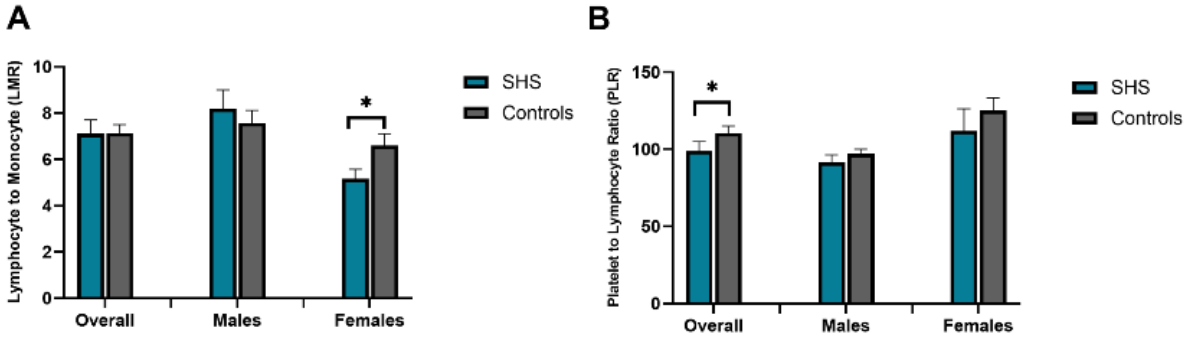

Figure 1. Comparison of the study variables between the passive smoking group and the control group—total sample, males, and females

Figure 1 (A): Show the Lymphocyte to Monocyte Ratio (LMR) across the overall sample, as well as the Male and Female groups; (B): Show the Platelet to Lymphocyte Ratio (PLR) across the overall sample, as well as the Male and Female groups; SHS: Secondhand Smoke: * Significant at P≤0.05.

3.3. Correlation Analysis between Duration of Passive Smoke Exposure and Study Indices

Pearson's correlation analysis revealed a statistically significant negative relationship between LMR and the duration of passive smoke exposure (r= −0.27, P = 0.047). In contrast, PLR showed no statistically significant correlation with exposure duration (r= 0.06, P = 0.867) (Table 3; Figure 2).

Table 3. Correlation coefficients (r) between the duration of passive smoke exposure and the inflammatory indices under investigation.

Parameters	Correlation coefficient-r	*P*-Value
LMR	-0.27	0.047*
PLR	0.06	0.867

r=Person Correlation Coefficient; P-Value calculated using Iindependent samples t-test; * Significant at P≤0.05

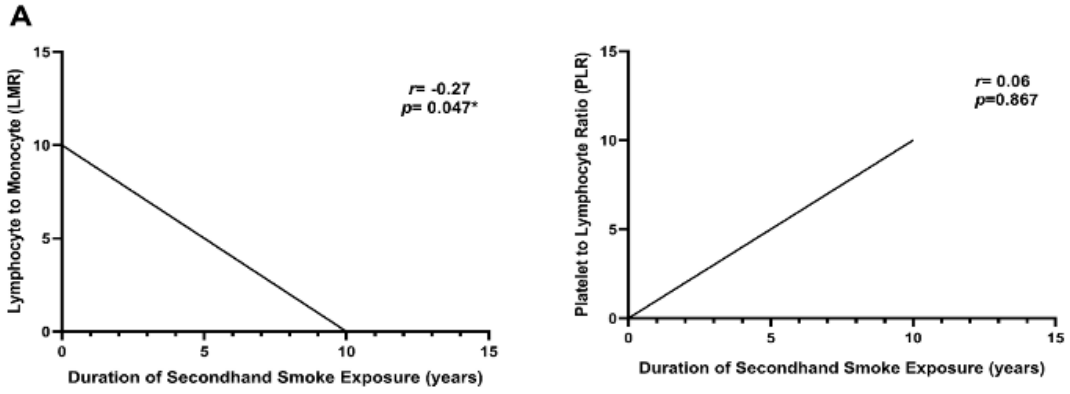

Figure 2. Correlation between the duration of passive smoke exposure and the inflammatory indices (LMR and PLR) in the passive-smoking group

Figure 2: illustrates Person correlation coefficients (r) between the duration of Secondhand Smoke (SHS) exposure (in years) and: (A) Lymphocyte to Monocyte Ratio (LMR), and (B) Platelet to Lymphocyte Ratio (PLR) for the Overall Sample; * Significant at $P \leq 0.05$.

4. Discussion

The aim of the present study was to record the LMR and PLR values in sex stratified group of passive smokers of the adult age and to study the relationship between these indices and the period of exposure to second hand smoke. We found a statistically significant decrease in LMR in passively exposed female only, but not passively exposed male group. PLR, on the other hand, was significantly reduced at the overall level, but not at the sex-stratified level. Additionally, LMR was negatively and significantly related to duration of exposure, while PLR was not. These are discussed in detail below.

After that, age and BMI were comparable between the two study groups (active smokers and healthy controls) ($P \geq 0.05$), supporting the interpretation that any subsequent differences in LMR and PLR between the two groups is due to the effect of passive smoke. This homogeneity is a scientific weight as BMI has been associated with platelet counts (Furuncuoğlu *et al.*, 2016), and LMR and PLR are prone to decline gradually with age (Luo *et al.*, 2019). It would have been much more difficult to be able to differentiate the specific impact of passive smoking if these two factors had not been well controlled.

The overall level comparison showed almost no difference between groups with a remarkably small *P* value of 0.989 for the lymphocyte to monocyte ratio (LMR). However, this near uniformity of the overall mean hides a substantive difference that only becomes apparent when the data are analyzed by sex. Specifically, compared to healthy female controls there was a clear and significant decrease in LMR for passively exposed females ($P = 0.030$), but a non significant increase for passively exposed males ($P = 0.237$). That is, a decrease in LMR was observed in females and a corresponding inverse (but not statistically significant) trend was observed in males. It is this sexual antagonism that made the sum of the two trend results appear to be null; when combined, the opposing trends effectively cancelled one another out. The scientific contribution of the present study is that it reveals a pattern which would remain completely hidden without stratification by sex, highlighting the importance of disaggregation in the study of smoking related inflammatory indices.

Comparisons of the control group values obtained in our study with the normative data of other investigations may be instructive to verify consistency with the knowledge available about these indices in healthy individuals. Contrary to a large study of Chinese reference children that reported an increase in LMR values for healthy females (Wang *et al.*, 2021), healthy males had higher LMR values in our cohort. This may be due to ethnic and/or population differences. On the other hand, the values obtained from our healthy control group were similar to a reference study conducted in Iranian population, which is closer to the ethnic group in the Iraqi study (Moosazadeh *et al.*, 2019), supporting our results and indicating the urgent need for reference values of Iraqi population.

This observed sex based divergence may be explained using insights from the well-established physiological differences in the effect of sex hormones on immune cells. Oestrogen increases the activity of lymphocytes, while at the same time decreasing the activity of monocytes, whereas the androgens directly inhibit the activity of monocytes and macrophages (Hoffmann *et al.*, 2023; Sciarra *et al.*, 2023). This could make it easier for monocytes in females to become truly activated during exposure to passive smoking, but the downside effect of testosterone in males prevents them from being activated. This is consistent with genomic evidence that indicates that female cells are far more affected by smoke exposure, with 61 genes being affected compared to 19 in males (Ashare & Wetherill, 2018) and the findings from wider epidemiological studies, where higher risks of ischaemic heart disease, chronic obstructive pulmonary disease, and stroke due to passive smoking are shown among females (Fischer & Kraemer, 2015). Additionally, the timing of blood sampling in relation to the menstrual cycle could be an additional source of variability for LMR in females, which was not controlled for in the present study (Nowak *et al.*, 2016).

Our findings of a reduction in LMR in the females are similar to the previous study that reported this correlation with smoking intensity among current smokers (Cekici *et al.*, 2019). But our finding is qualitative novelty because it shows that even in the less intense scenario of passive smoking, the loss of LMR is more in females than males.

With respect to PLR, we saw a statistically significant drop at the overall level (P = 0.049), but that was not the case in either of the sex-specific subgroups (males, P = 0.381; females, P = 0.092), although the trend was always negative in both. This trend is most likely due to the reduced statistical power as a consequence of sample subdivision, as the P value was close to the accepted threshold of 0.05, suggesting a real effect which would need increased sample numbers to be confirmed. The result is added significance of these two indices in various other circumstances. In patients with myocardial infarction, low LMR has been linked to a higher risk of mortality and cardiac events (Gu *et al.*, 2025); in coronary artery disease it is associated with higher risk of mortality and cardiac events (Vakhshoori *et al.*, 2023); and in ischaemic stroke, it is associated with higher risk of mortality and cardiac events (Tian *et al.*, 2025). Similarly, PLR has been shown to have predictive value in breast cancer (Zhao *et al.*, 2025) and LMR is still a prognostic index in larger panel of systemic inflammatory indices, including SII and SIRI, in diabetic patients (Cosma Lăzuran *et al.*, 2025). This cross specialty validation enhances the confidence in their use to passive smoking. The overall PLR reduction we recorded is similar to that reported by Gumus *et al.* (2018) in smokers, who showed a marked reduction in PLR among active smokers suggesting that passive smoking also may induce the same systemically observed platelet lymphocyte redistribution.

We have included additional evidence in our correlation analyses that the changes of these indices are a true response to exposure and not random variation. LMR showed a significant and negative correlation with duration of passive smoking ($r = -0.27$, $P = 0.047$), which is similar to the dose response relationship found in active smoking studies (Yao *et al.*, 2025) and the similar correlation with smoking intensity reported in passive smoking studies (Cekici *et al.*, 2019). In contrast, there was no statistically significant association between PLR and exposure duration ($r = 0.06$, $P = 0.867$). This could imply that changes in PLR are early in life and become fixed, or that the number of years of exposure is not as accurate as the pack year approach employed in active smoking studies. The interpretation of this dosage is supported by smoking cessation studies that document that similar haematological inflammatory indices (HII) have shown a clear decrease following smoking cessation (Komiyama *et al.*, 2021) leading to the future research question of reversibility of these LMR changes upon cessation of passive exposure.

To conclude, there is a systemic inflammatory footprint from passive smoking detectable by LMR and PLR, with a sex- and exposure duration-dependent nature and intensity. The effect of the two is greatest for females when considering LMR and for PLR when considering the overall level, but not in each subgroup of males and females. To our knowledge, this is the first study to compare both indices together and in the context of passive smoking using a sex–stratified approach. They call into question the value of using only a single level of analysis in investigating these markers, and suggest that more extensive future research is needed to confirm the consistency of this trend.

Limitations

There are a number of limitations of the generalisability. A relatively small number of participants in the analysis (58, sometimes as few as 10 for sex stratified analysis) may have reduced the statistical power required for significance conclusions in sex stratified PLR analysis. Convenience sampling from one governorate also reduces the extent to which our findings can be generalized. An inherent property of the cross sectional design makes it impossible to conclude any causal inferences. In addition, we did not have objective biochemical confirmation of the duration of exposure in the form of cotinine; this may create recall bias. Last, the number of neutrophils was not measured and therefore the NLR index could not be calculated; also, the phase of the menstrual cycle was not controlled for in women subjects when taking blood samples.

Conclusion

This research finds that passive smoking does not produce a consistent inflammatory response in males and females. The effect was clearly visible in LMR in females specifically while the effect in PLR was only at the aggregate level. This gap has a methodological message for this study and for any future research on smoking-related inflammatory indices: Failure to consider sex based stratification may mask rather than reveal true patterns in the study. Practically speaking, from a scientific point of view, LMR becomes more attractive as the screening tool for the passively exposed woman, at least until the results are confirmed in larger, multicentre sets of women before clinical use is considered.

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