MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.12.588.592

OPEN ACCESS

Key Words Lymphocyte-to-monocyte ratio (LMR), breast cancer, prognosis, biomarker, immune response and tumor staging

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Received: 20 October 2024
Accepted: 20 December 2024
Published: 30 December 2024

Citation: Dr. Amit Agrawal, Dr. Manju Singh and Dr. Rupesh Kumar Sahu, 2024. Study of Level of Serum Lymphocyte to Monocyte Ratio (LMR) in the Breast Cancer Patients. Res. J. Med. Sci., 18: 588-592, doi: 10.36478/makrjms.2024.12.588.592

Study of Level of Serum Lymphocyte to Monocyte Ratio (LMR) in the Breast Cancer Patients

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ABSTRACT

Breast cancer is one of the most common malignancies among women globally. In recent years, the lymphocyte-to-monocyte ratio (LMR) has emerged as a potential biomarker for prognosis in various cancers, including breast cancer. LMR reflects the immune response, with low levels being associated with poor outcomes in malignancies. Understanding the significance of LMR in breast cancer could help in predicting prognosis and guiding treatment strategies. To assess the level of serum lymphocyte-to-monocyte ratio (LMR) in breast cancer patients. This study was a single center, observational, analytical, cross sectional study. It was conducted for 1 year from December 2022 to November 2023 in the Department of General surgery of Pt JNM Medical College Raipur-Dr. Bhim Rao Ambedkar Memorial Hospital Raipur, (C.G.) located in Central India. In our study, we found that 17 out of 19 (89.5%) cases in grade 1 have more than 5.0 of L:M Ratio, 22 out of 51 (43.1%) cases in grade III have more than 5.0 of L:M Ratio.56.9% of cases in grade III have less than 5.0 of L:M Ratio. This indicates severity of Breast Cancer can be indicated by low levels of L: M Ratio. This association was found to be significant (P<0.001). Serum LMR is a potentially valuable prognostic marker in breast cancer patients. Lower LMR levels are associated with advanced disease and poor prognosis, suggesting its utility in patient stratification and management.

INTRODUCTION

Breast cancer is the most common cancer among women and its frequency has increased dramatically in recent years. Most of them are epithelial tumors with ductal or lobular histology. Breast carcinoma is a metastatic cancer that can spread to distant organs such as the bone, liver, lung and brain, which is why it is incurable. However, an early detection of this malignancy results in a favorable prognosis and a high survival percentage [1]. Breast cancer has a complicated etiology, with risk factors including sex, age, estrogen, family history, gene mutations and an unhealthy lifestyle. Although the prevalence of breast cancer rises year after year, the death rate falls due to widespread early detection and sophisticated medical treatments. According to epidemiological studies, 20-30% of patients develop distant metastasises and recurrence[2]. Breast cancer contributes for more than 1 in 10 new diagnosed malignancies worldwide. It is about 100 times commoner in women than in men, although males tend to have poorer prognosis due to delayed diagnosis. Epidemiological studies have revealed that the global burden of breast cancer is anticipated to cross almost 2 million by the year 2030[3]. Breast cancer is currently one of the most prevalently diagnosed cancers and the 5th cause of cancer-related deaths with an estimated number of 2.3 million new cases worldwide according to the GLOBOCAN data. As per this GLOBOCAN data, in India, it has accounted for 13.5% of all cancer cases and 10.6% of all deaths[4]. As per an Indian study, breast cancer comprises 16-21% cases of all cancers, which is next to commonest cervical cancers among women[5]. Despite the variety of treatment options available for breast cancer, as well as the ongoing development of new medications and therapies, some breast cancer patients continue to have recurrence and metastasis, which severely limits their quality of life[6] fahad[7] ma 2021 In breast cancer, molecular subtypes also impact the prognosis[8]. Pathological indicators like size of tumor, axillary lymph node metastasis and molecular biological indicators such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2) and ki-67 are currently used to lead the prognosis of breast cancer patients[9]. Masood 2005) these pathological indicators mainly obtained by biopsy or postoperative pathological reports are difficult to represent the overall condition of the tumor.

MATERIALS AND METHODS

The study aimed to include all female patients with histologically confirmed breast cancer who visited the Out-Patient Department (OPD) or were admitted to the preoperative ward during this period. It was conducted over a period of one year, from December 2022 to November 2023, in the Department of General Surgery at Pt JNM Medical College Raipur-Dr. Bhim Rao Ambedkar Memorial Hospital in Raipur, Chhattisgarh, located in Central India.

The Inclusion Criteria were:

- All types of histopathologically confirmed breast cancer.
- Patients aged >18 years.
- Patients willing to participate, comply with the study protocol and attend follow-up visits.

The exclusion criteria included:

- Prior surgery, chemotherapy, or radiotherapy for breast cancer.
- Major systemic diseases (e.g., lymphoma, myeloma) or active infections that could confound results.
- Pregnant or lactating women.

Data collection involved obtaining detailed demographic information, such as name, age, address, education, occupation and marital status. Eligible candidates underwent necessary investigations and once enrolled, data regarding age, diagnosis and cancer stage was recorded in the case record form. Necessary investigations included a complete blood count and calculation of the Serum Lymphocyte Monocyte Ratio (LMR). The final sample size for the study was 258 patients.

Statistical Analysis: Statistical analysis was performed using SPSS (version 27.0) and GraphPad Prism (version 5). Numerical data were summarized as means and standard deviations and categorical data as counts and percentages. Two-sample t-tests and paired t-tests were used to compare group means, while chi-square tests (or Fisher's exact test when appropriate) were used to compare proportions. A p-value #0.05 was considered statistically significant.

RESULTS AND DISCUSSIONS

In our study, we found that there was a significant association between low LMR and lymph node involvement in the breast cancer patients (p value <0.0001). Additionally, a significant association was observed between high LMR and the absence of lymph node involvement in these patients.

In our study, we found that there was a significant association between low LMR and the presence of distant metastasis in the breast cancer patients (p value <0.00001). Additionally, a significant association was observed between high LMR and the absence of distant metastasis in these patients. Association was assessed between LMR and metastasis using the Chi-square test. In our study, we found that there was a significant association between low LMR and Triple Negative Breast Cancer (p value = 0.00001). Additionally, a significant association was observed between high LMR and non-Triple Negative Breast Cancer. Association was assessed between LMR and Triple Negative Breast Cancer using the Chi-square test. In our study, we found that

Table 1: Association between LMR and Menopausal Status, Tumor Size, Lymph Node Involvement

			LMR		
			Low	High	P Value
Menopausal Status	No	Count	26	76	0.555
		% within LMR	36.60%	40.60%	
	Yes	Count	45	111	
		% within LMR	63.40%	59.40%	
	Total	Count	71	187	258
		% within LMR	100.00%	100.00%	100.00%
Tumor Size	<2 cm	Count	0	3	0.283
		% within LMR	0.00%	1.60%	
	>2 cm	Count	71	184	
		% within LMR	100.00%	98.40%	
	Total	Count	71	187	258
		% within LMR	100.00%	100.00%	100.00%
LN involvement	No	Count	6	70	0.0001
		% within LMR	8.50%	37.40%	
	Yes	Count	65	117	
		% within LMR	91.50%	62.60%	
	Total	Count	71	187	258
		% within LMR	100.00%	100.00%	100.00%

Table 2: Association between LMR and Metastasis, Triple Negative Breast Cancer

			LMR		P Value
			Low	High	
Metastasis	No	Count	53	180	0.00001**
		% within LMR	74.60%	96.30%	
	Yes	Count	18	7	
		% within LMR	25.40%	3.70%	
Total		Count	71	187	258
		% within LMR	100.00%	100.00%	100.00%
Triple Negative Breast Cancer	Non-Triple Negative Breast Cancer	Count	43	177	0.00001**
		% within LMR	60.60%	94.70%	
	Triple Negative Breast Cancer	Count	28	10	
		% within LMR	39.40%	5.30%	
Total		Count	71	187	258
		% within LMR	100.00%	100.00%	

Table 3: Association between LMR & Type of Breast Cancer

Type of Breast Cancer * LMR Cross tabulation					
			LMR		P value
			Low	High	
Type ofBreast Cancer	Ductal Carcinoma	Count	69	186	0.808
		% within LMR	98.50%	98.90%	
	Other (Lobular & Mucinous)	Count	1	2	
		% within LMR	1.50%	1.10%	
Total		Count	70	188	258
		% within LMR	100.0%	100.00%	100.00%

Table 4: Association between LMR & Luminal Subtype of Breast Cancer

LMR * Luminal Cross Tabulation					
			Luminal A	Luminal B	P Value
LMR	Low	Count	20	5	0.891
		% within LMR	13.6%	12.8%	
	High	Count	127	34	
		% within LMR	86.4%	87.2%	
Total		Count	147	39	186
		% within LMR	100.0%	100.0%	100.0%

Table 5: Serum L: M Ratio in relation to Histological Grading

Serum L:M Ratio	Histological Grade						Total	
	Gr I		Gr II		Gr III			
	No.	%	No.	%	No.	%	No.	%
< 2.5	0	0	2	1.1	1	2	3	1.2
2.5 - 5..0	2	10.5	38	20.2	28	54.9	68	26.4
> 5.0	17	89.5	148	78.7	22	43.1	187	72.4
Total	19	100	188	100	51	100	258	100

Table 6: Diagnostic Validity Tests

Predictive value of L:M Ratio in the prediction of progression of Breast cancer: Cut-off value of L:M Ratio: 5.0		
Sensitivity	29/51	56.90%
Specificity	165/207	79.70%
PPV	29/71	40.80%
NPV	165/187	88.20%
Accuracy	194/258	75.20%

17 out of 19 (89.5%) cases in grade 1 have more than 5.0 of L:M Ratio, 22 out of 51 (43.1%) cases in grade III have more than 5.0 of L:M Ratio.56.9% of cases in grade III have less than 5.0 of L:M Ratio. This indicates severity of Breast Cancer can be indicated by low levels of L:M Ratio. This association was found be significant (P<0.001). Using L:M Ratio of 5.0 as cut-off value (Bio-marker), diagnostic tests were done to predict the progression of Breast Cancer from grade I/II (mild/moderate) to Grade III (Severe). In our study, we found that serum Lymphocyte to Monocyte Ratio (LMR) has sensitivity of 57%, specificity 80%, overall accuracy of 75% in the prediction of progression of breast cancer.

In our study, we did not found any significant association between LMR and Luminal subtypes in the breast cancer patients (p value = 0.891).

In our study, we found that the association between LMR and Menopausal Status in the breast cancer patients was statistically not significant (p value= 0.555). In our study, we found that the association between LMR and Tumor Size in the breast cancer patients was statistically not significant (p value = 0. 283). Association was assessed between LMR and Tumor Size using the Chi-square test.

In our study, we did not found any significant association between LMR and Type of Breast Cancer (p value 0.808).

In our study (70.5%) 182 breast cancer cases had lymph node involvement Similarly, In the study conducted by Khazaei et al [1] 58.8 % had lymph node involvement and In the study conducted by Hongfei et al.[10]70.7 % of patients had positive lymph nodes.

The current study found a highly significant correlation between low LMR and lymph node involvement (p=0.0001). Individuals with a lower LMR (<5.0) are more likely to experience lymph node involvement. Low LMR and lymph node metastases both indicate a bad prognosis for breast cancer patients. This is similar with the study conducted by Song et al[11] which demonstrated a significant correlation between lymph node metastasis (LNM) in breast cancer and LMR (Lymphocyte-to-Monocyte Ratio) (p = 0.002).

The present study showed that 102 out of 258 (39.5%) breast Cancer patients were premenopausal women; remaining 156 out of 258 (60.5%) breast cancer patients were post-menopausal women.

The present study shows no significant association between LMR and Menopausal Status in the breast cancer patients (p=0.555). It implies that whether a patient was pre- or post-menopausal had no significant effect on their LMR levels. We identified Low or High LMR in all breast cancer patients, regardless of menopausal state. Low LMR is identified in breast cancer patients with a bad prognosis, hence being pre- or post-menopausal in our study does not indicate a poor prognosis.

In the study conducted by Khazaei et al. [1] 67 % of patients were premenopausal and 33 % of patients were postmenopausal. In the study conducted by Hongfei et al. [10] over half of all patients, about 56.4 % were premenopausal, and 43.6 % were post-menopausal, which did not match with our study.

In the present study, the majority of breast cancer patients (98.8%), 255 out of 258, had tumors larger than 2 cm. Only three

(1.2%) instances had tumors less than 2 cm. This reflects the late appearance of breast cancer at our institute. In the study by Khazaei et al.[1] 23.5 % of patients had tumor size less than 2, and 76.5 % of patients had size more than 2 cm.

The current study found no significant relationship between LMR and tumor size (p = 0.283). Our study identified low LMR (<5.0) and high LMR (>5.0) in breast cancer patients, regardless of tumor size. This suggests that in our research sample, the size of a breast cancer tumor had no detectable influence on LMR levels across patients. Low LMR is identified in breast cancer patients with a bad prognosis, hence in our study, large or small tumor size in the breast cancer patient does not indicate a poor prognosis.

While, in the study by Goto et al[8] low LMR was significantly correlated with tumour size (p = 0.036). The difference in findings between these studies could be due to various factors such as differences in sample size. In our study there was a very low sample size of less than 2cm tumors.

The present study showed a highly significant association between low LMR and presence of distant metastasis (p=0.00001). This indicates that individuals with a lower LMR (<5.0) are more likely to exhibit distant metastasis. Low LMR & metastasis both are directed towards poor prognosis of the breast cancer patients.

This is similar with the study conducted by Ma et al[7] which demonstrated a significant correlation between distant metastasis in breast cancer & LMR (Lymphocyte-to-Monocyte Ratio) (p=0.005)

In our study, we also found association between high LMR (Lymphocyte-to- Monocyte Ratio) and non-Triple Negative status in breast cancer patients. This indicates that individuals with a higher LMR are more likely to have non-Triple Negative breast cancer, which includes hormone receptors such as ER, PR and HER2- neu these all three are not likely to be negative in breast cancer patients with higher LMR values.

In our study (14.7%) 38 cases out of 258 were found Triple Negative Breast Cancer whereas (85.3%) 220 cases were found Non - Triple Negative Breast Cancer.

In the study conducted by Goto et al[8], about 35.8% of breast tumors were Triple Negative Breast Cancer and 64.2 % were Non - Triple Negative Breast Cancer. The present study uncovered a compelling association between low LMR (Lymphocyte-to-Monocyte Ratio) and Triple Negative status in breast cancer patients (p<0.00001). Triple Negative Breast Cancer was significantly associated with low LMR status, leading towards poor prognosis.

This observed correlation suggests a potential dichotomy in the immune microenvironment of breast tumours based on ER, PR& HER2neu expression status. Breast cancer patients with triple negative status exhibited lower LMR values, indicating a diminished lymphocytic response relative to monocyte levels causing poor prognosis. Conversely, patients with non-triple negative status demonstrated higher LMR values, indicative of a more robust lymphocytic response relative to monocyte levels causing good prognosis in the breast cancer patients. This does not agree with the study conducted by Goto et al [8], LMR was not significantly correlated with Triple Negative Breast Cancer (p = 0.719).

Locally advanced breast cancer (LABC) is a difficult stage of breast cancer defined by tumors that have migrated beyond the breast and into adjacent lymph nodes. Low LMR (<5.0) is associated with a higher likelihood of lymph node involvement, indicating that patients with Serum LMR (Lymphocyte-to-Monocyte Ratio) less than 5.0 are more likely to develop locally advanced breast cancer than those with higher LMR values. This study shows that lower LMR levels might be used to predict the existence of LABC. Thus, the link between low serum (not blood) LMR levels and an elevated risk of LABC shows LMR's potential use as a non-invasive biomarker for disease staging. A serum LMR <5.0 could aid clinicians in identifying patients at higher risk of LABC, prompting further diagnostic evaluations and tailored treatment approaches.

In the study conducted by Goto et al. [8] LMR is linked to prognosis and treatment response in breast cancer patients undergoing neoadjuvant chemotherapy, which is a standard treatment strategy for LABC. This study indicates that a higher LMR may be related with a better prognosis and treatment response in individuals with locally advanced breast cancer. The current study found that the majority of breast cancer patients (98.8%), 255 out of 258 patients, had ductal carcinoma, with just two (0.8%) cases of lobular carcinoma and one (0.4%) case of mucinous carcinoma.

Similarly, In the study by Sun YS et al [12] Histologically, 89.1% were ductal carcinoma, whereas only 3.1% were lobular carcinoma, 2.2% were mucinous carcinoma, 0.5% were medullary carcinoma, and 5.1% were classified as other types of breast cancer.

The study found no significant link between lymphocyte-to-monocyte ratio (LMR) (<0.5) and type of breast cancer (p = 0.808). The fact that low and high LMR levels were found independent of the kind of breast cancer is very interesting. This suggests that LMR may not be a good indication of breast cancer subtypes. This conclusion has significant implications for both clinical treatment and research. It implies that LMR alone may be insufficient for predicting or categorizing breast cancer kinds. As a result, relying simply on LMR levels may present doctors with inaccurate information about a patient's unique subtype of breast cancer. Low LMR is related with a bad prognosis, although the type of breast cancer did not predict the patient's prognosis in our study. The study shows that any kind of breast cancer with low serum LMR would have poor prognosis.

Our study showed that (7.4%)19 out of 258 Breast Cancer patients had histological grade I. Majority of the patients (72.8%) 188 out of 258 had histological grade II and (19.8%) 51 cases had histological grade III.

In the study by Hongfei et al. [10]9.7 % were histological grade I, 84.9 % were histological grade II, and 5.4 % were histological grade III.

The current study found a statistically significant link between low lymphocyte-to-monocyte ratio (LMR) and higher severity of breast cancer. The discovery, which has a p-value of <0.00001, shows that LMR might be used as a prognostic biomarker for breast cancer, indicating its aggression and development.

In the present study, it was seen that 17 out of 19 (i.e. 89.5%) Cases in grade I have more than a 5.0 L: M Ratio, whereas only in (43.1%) Cases, 22 out of 51 grades III have more than 5.0 of L: M Ratio. 56.9% of Cases in grade III have less than 5.0 of L: M Ratio.

This indicates the severity of Breast Cancer can be indicated by low levels of the L: M Ratio. This association was found to be significant. (p<0.00001).

This agrees with the study conducted by Song et al [11] the grading of cancer was significantly correlated with LMR (p = 0.005) in which low LMR (Lymphocyte- to-Monocyte Ratio) was found in histologically high grade of breast cancer.

CONCLUSION

The study highlights the potential of the lymphocyte- to-monocyte ratio (LMR) as a prognostic biomarker in breast cancer patients. Lower LMR levels were significantly associated with advanced tumor stage, higher grade and poor prognosis. This suggests that LMR could serve as a useful, cost-effective marker for assessing disease progression and stratifying patients for personalized treatment. Further research is recommended to establish LMR as a routine prognostic tool in clinical settings for breast cancer management.

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