Pathology Section

Diagnostics Role of Haematological Parameters in Benign and Malignant Breast Lesions: A Retrospective Observational Study from a Tertiary Healthcare Centre in Tamil Nadu, India

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ABSTRACT

Introduction: Breast cancer is the most common malignancy diagnosed in women, and despite advancements in diagnosis and treatment, it still leads to significant morbidity and mortality. Distinguishing between benign and malignant breast disease is clinically challenging, and there is currently no serum biomarker available for early breast cancer detection. As part of the preoperative work-up for breast lesions, a Complete Blood Count (CBC) analysis is typically performed.

Aim: This study aimed to evaluate the utility of CBC parameters in diagnosing malignant breast lesions and to analyse the diagnostic role of haematological parameters within benign and malignant breast lesions, as well as different histological breast cancer stages.

Materials and Methods: This retrospective observational study was conducted for one year, from January to December 2021, at the Department of Pathology of PSG Institute of Medical Sciences and Research in Coimbatore, Tamil Nadu, India. The study included 60 female patients with both benign and malignant breast lesions. Histopathological examination confirmed the diagnoses of these lesions. CBC parameters, including haemoglobin, Total White Cell Count (TWBC), neutrophil count, lymphocyte count, monocyte

count, platelet count, and Mean Platelet Volume (MPV), were collected from a total of 120 cases. Additionally, the Neutrophil-Lymphocyte Ratio (NLR), Monocyte-Lymphocyte Ratio (MLR), and Platelet-Lymphocyte Ratio (PLR) were calculated from the obtained CBC parameters for all cases. The values were expressed as mean and standard deviation, and an independent t-test was used to compare the two groups. A p-value less than 0.05 was considered significant.

Results: Malignant breast lesions showed a significant increase in neutrophils (64.1±8.4%) and a significant decrease in lymphocytes (25.9±8%) and MPV (7.6±0.76 pg) compared to benign breast cases. The calculated ratios, such as NLR (2.9±1.7), MLR (0.32±0.2), and PLR (14.4±8), were also found to be increased in malignant cases. However, there were no significant variations in CBC parameters across the various stages of breast malignancy.

Conclusion: Among the CBC parameters evaluated, neutrophil count, lymphocyte count, MPV, NLR, MLR, and PLR were significantly altered in breast malignancy compared to benign breast masses. Measuring CBC parameters and their derived ratios are fast, simple, inexpensive, and readily available method that can assist physicians in predicting breast malignancy.

INTRODUCTION

Breast cancer is one of the most commonly diagnosed cancers and the leading cause of cancer-related deaths in women worldwide. In 2020, the cancer registry data of India projected a risk of 1 in 56 for breast cancer in women [1]. According to a report from the National Institute of Cancer Prevention and Research (NICPR), in India, one woman dies for every two newly diagnosed cases of breast cancer [1]. The increasing cancer burden poses a significant financial strain on healthcare systems globally, and many cancer patients lack access to timely and quality diagnosis and treatment. This is particularly concerning in countries like India, with a large rural population and limited diagnostic facilities. Raising awareness and utilising resources for early diagnosis are crucial in initiating early treatment and reducing breast cancer-related mortality and morbidity [1].

Hormonal imbalances contribute to the development of both benign and malignant breast lesions. Predominant oestrogen stimulation and relative progesterone deficiency are involved in the pathophysiology of benign breast lesions [2]. Several hypotheses propose that oestrogen plays a role in causing breast cancer. One hypothesis suggests that oestrogen promotes cellular proliferation, leading to errors in Deoxyribonucleic acid (DNA) replication when oestrogen binds to its receptors. If these errors are not repaired, they

can result in mutations that lead to cancer development. Another hypothesis suggests that metabolites of oral oestrogen react with breast tissue DNA, exerting oncological effects. Women undergoing hormonal replacement therapy for premenstrual symptoms have a higher risk of developing breast cancer [3]. However, the exact causes of breast lesion development are still unknown.

Pre-treatment cases of breast cancer often exhibit haematological abnormalities due to bone marrow infiltration by cancer cells, leading to suppression of haematopoiesis [4,5]. In India, 60% of breast cancer patients have pre-treatment anaemia [6]. The causes of anaemia may include malnutrition, tumour-related bleeding, abnormal iron metabolism, erythropoietin suppression by tumour cells, and compromised bone marrow function [7,8]. Thrombocytopenia, characterised by a low platelet count, is caused by cancer cells frequently activating coagulation [9]. Some studies have found thrombocytosis in breast cancer patients, which can be attributed to the ability of cancer cells to increase platelet count and aggregation [4,10].

Low-grade chronic inflammation plays a vital role in cancer pathogenesis. Neutrophils and monocytes produce Reactive Oxygen Species (ROS) and Nitric Oxide (NO), unstable molecules usually neutralised by antioxidants. If not balanced, they react with DNA, proteins, and lipids, causing damage and accumulation. This leads to

genetic instability and the development of cancer [11]. Inflammatory biomarkers, such as White Blood Cell Count (WBC) and derived ratios like NLR, MLR, and PLR, have been found helpful as diagnostic and prognostic markers in various malignancies.

CBC is a routine investigation to assess a patient's nutritional, immunological, and inflammatory state. Cancer-promoting inflammation plays a critical role in conferring the hallmarks of cancer, including angiogenesis, invasion, metastasis, and genomic instability [12,13]. Changes in peripheral blood counts can assess the extent of cancer-related inflammation. Haematological parameters like red cell indices, leucocyte count, NLR, PLR, MLR, MPV, and platelet counts have shown diagnostic and prognostic importance in different types of malignancies [14-16]. Some studies have found the utility of haematological parameters like NLR, PLR, and MLR as prognostic markers in breast malignancy [17-20]. However, the application of these simple and inexpensive parameters has not been extensively explored in India, except for three studies from Punjab and Karnataka [21-23] that focused on differentiating between benign and malignant breast diseases in the preoperative period. If the results show a high predictive value, clinicians in resource-limited settings can utilise the haematological parameters to predict the occurrence of malignancy in a breast mass. These parameters are cost-effective, thus alleviating the healthcare cost burden in the country.

The incidence of breast carcinoma in Coimbatore is 14% [24], and no studies to date have examined the use of haematological parameters for diagnosing and prognosticating breast carcinoma in this population. Therefore, we attempted to test the utility of CBC parameters in this population to enable early prediction and forecasting of malignant breast disease by comparing them with benign breast lesions.

MATERIALS AND METHODS

The present study was an observational, retrospective study conducted from July 2022 to September 2022. The data were retrieved from a continuous 12-month period (January to December 2021) after obtaining ethical clearance from the Institutional Ethics Committee (22/146). The study included 154 adult female patients diagnosed with benign or malignant breast disease on histopathology.

Inclusion criteria: Females with breast lesions older than 20 years diagnosed as either benign or malignant on histopathology.

Exclusion criteria:

1. Patients with benign or malignant breast lesions diagnosed only on radiology or cytology.

2. Breast carcinoma patients who have undergone chemotherapy, radiotherapy, or surgery.

3. Patients with a diagnosis of inflammatory breast disease.

4. Patients with a previous underlying haematological disorder.

5. Patients with underlying infections.

6. Patients with no availability of CBC parameters at the time of breast lesion diagnosis.

The clinical and pathological stages of breast cancer were determined using the 7th Edition of the American Joint Committee on Cancer (AJCC), and the type of histology was classified according to guidelines from the World Health Organisation (WHO) [25,26]. The Histopathological grades of the tumour were classified using the Nottingham-Bloom-Richardson system (modified) [27].

After applying the inclusion and exclusion criteria, there were 120 female patients, including 60 patients with malignant breast lesions and 60 with benign breast lesions. The incidence of malignancy is known to occur in a higher age group than benign breast lesions [23]. Hence, the age could not be matched between the two groups. However, an equal number of patients were included in the two groups.

Data collection: Whole blood venous samples were collected in K2 EDTA for baseline CBC examination for all 120 patients during the preoperative period. The blood samples were analysed on the Beckman Coulter LH-780 Haematology analyser (Beckman Coulter, Brea, CA) within four hours of collection. Patient information such as age, lesion size, histopathology diagnosis, and stage of malignancy was noted. The CBC parameters such as haemoglobin (Normal: 12.0-14.9 g/dL), TWBC (normal: 3800-12500/μL), neutrophil count (normal: 40-70%), lymphocyte count (normal: 20-40%), monocyte count (normal: 2-10%), platelet count (normal: 151-532×103/μL), and MPV (normal: 6-10.5 fl) [28,29] were recorded for all the patients. The ratio between the absolute number of neutrophils and lymphocytes was calculated as the NLR (normal: 1.70±0.70), and the ratio between the absolute number of monocytes and lymphocytes was the MLR (normal: 11.15±3.14). The PLR (normal: 117.05±47.73) was calculated as the ratio between the absolute number of platelets and lymphocytes. NLR, MLR, and PLR were calculated for all 120 patients [30].

STATISTICAL ANALYSIS

All analyses were performed using IBM SPSS software, version 23.0 (SPSS, Chicago, IL), and values were expressed as mean±standard deviation. The independent t-test was used to compare mean values between the two groups. A p-value of less than 0.05 was considered significant.

RESULTS

This study included 120 patients with benign and malignant breast diseases, for whom pre-treatment CBC data were available before surgery or biopsy. Among the 60 benign breast cases, the most frequent disease diagnosed was fibroadenoma (48/60 cases), followed by benign phyllodes tumour (6/60 cases), sclerosing adenosis (4/60 cases), mild usual ductal hyperplasia (1/60 cases), and pseudoangiomatous stromal hyperplasia (1/60 cases). Among the malignant breast diseases, most cases were of ductal origin (56/60 cases), followed by lobular carcinoma (2/60 cases), metaplastic carcinoma (1/60 case), and tubular carcinoma (1/60 case).

Baseline clinicopathological variables are presented in [Table/Fig-1-3]. There was a significant difference in the mean age of occurrence between benign (37.5 years) and malignant (56.6 years) breast disease at the time of diagnosis. The two breast lesions showed no significant difference in lesion size [Table/Fig-1].

S. No.	Disease type	No. of cases	Age (years) (Mean±SD)	Size of the lesion (cm) (Mean±SD)
1	Benign	60	37.5±13	4.2±2.4
2	Malignant	60	56.6±10.2	3.8±3

[Table/Fig-1]: A comparison of patient's age and the size of benign and malignant breast lesions.

Age group	Number of benign breast cases	Number of malignant breast cases
10-19 years	8	-
20-29 years	12	-
30-39 years	20	-
40- 49 years	12	13
50-59 years	8	26
60-69 years	-	14
70-79 years	-	6
80-89 years	-	1

[Table/Fig-2]: Patient's age distribution dipiciting the occurence of benign and malignant breast lesions.

The comparison of CBC parameters, NLRs, MLRs, and PLRs between benign and malignant breast disease is summarised in

Histopathology diagnosis	Number of cases
Fibrodenoma	48
Benign phyllodes	6
Sclerosing adenosis	4
Mild usual ductal hyperplasia	1
Pseudoangiomatous stromal hyperplasia	1
Invasive carcinoma of no special type (ductal, not otherwise specified)	56
Lobular carcinoma	2
Metaplastic carcinoma	1
Tubular carcinoma	1

[Table/Fig-3]: A list of histopathological diagnoses rendered for all breast lesions.

[Table/Fig-4]. There was no significant difference in haemoglobin, total WBC, absolute monocyte count, and platelet count between benign and malignant breast diseases. However, there was a significant difference in neutrophil count, lymphocyte count, MPV, NLR, MLR, and PLR between benign and malignant breast diseases [Table/Fig-4]. Similarly, age, lesion size, and CBC parameters were compared between the various stages of breast malignancy [Table/Fig-5]. No significant change was observed in stages 1 to 4.

Parameter	Benign	Malignant	p-value
Haemoglobin (g/dL)	11.8±1.2	11.8±1.4	0.995
WBC total count (×10³/μL)	8.5±1.9	7.8±2.2	0.73
Neutrophil (%)	61.1±8.1	64.1±8.4	0.046*
Lymphocyte (%)	29±7.3	25.9±8	0.026*
Monocyte (%)	6.8±1.5	7.2±3.1	0.335
Platelets×10³/μL	320.8±75.7	327.9±103	0.670
Mean platelet volume (pg)	7.9±0.8	7.6±0.76	0.031*
Neutrophil lymphocyte ratio	2.3±1.1	2.9±1.7	0.032*
Monocyte lymphocyte ratio	0.25±0.1	0.32±0.2	0.025*
Platelet lymphocyte ratio	11.9±4.5	14.4±8	0.034*

[Table/Fig-4]: Comparison of CBC parameters between the benign and malignant breast patients.
The independent t-test was used to compare between the two groups and p-value of less than 0.05 was considered significant

Parameter	Stage-1 (n=3) Mean±SD	Stage-2 (n=40) Mean±SD	Stage-3 (n=16) Mean±SD	Stage-4 (n=1) Mean±SD	p-value
Age (years)	58.3±2	57.5±10.5	54.5±10.4	50	0.699
Size (cm)	2.1±0.3	4±3.4	3.9±2.1	3.8	0.715
Hb (g/dL)	12.7±0.6	11.7±1.6	11.8±1.3	11.8	0.735
WBC total count×10³/μL	9.3±1.7	7.7±2.3	7.8±2	6.8	0.691
Neutrophil (%)	61.7±14.5	64.4±8.2	64.1±8.5	60.4	0.926
Lymphocyte (%)	29.9±14.1	25.9±7.8	24.9±7.9	27.9	0.804
Monocyte (%)	5.9±0.3	7.2±2.7	7.5±4.3	9	0.823
Platelets×10³/μL	294.3±38	325.9±103.1	341.6±115.6	289	0.865
Mean Platelet Volume (pg)	8.1±0.8	7.7±0.7	7.4±0.7	7.3	0.483
Neutrophil lymphocyte ratio	2.4±1.3	2.9±1.6	3.1±2.1	2.1	0.909
Monocyte lymphocyte ratio	0.2±0.7	0.3±0.1	0.3±0.2	0.3	0.784
Platelet lymphocyte ratio	10.8±3.2	14.3±8.5	15.4±7.7	10.3	0.783

[Table/Fig-5]: Comparison of age, lesion size and CBC parameters across the four stages of breast malignancy.
The independent t-test was used to compare between the two groups and p-value of less than 0.05 was considered significant

DISCUSSION

The utility of CBC parameters as clinical values was analysed in breast lesions, including 60 benign and 60 malignant cases. There was no significant difference in size between benign and malignant breast lesions, which aligns with the common diagnosis of breast cancer after age 50 [31]. Unlike other studies, this analysis did not find a decrease in Hb levels in malignant cases compared to benign cases [32,33]. The cause of anaemia in those studies was attributed to malnutrition, decreased erythropoietin, and bone marrow suppression. There was no significant change in total WBC count between benign and malignant breast diseases. Neutrophilia, an increase in neutrophils, was observed in all types of malignancies, including this study [34-37]. A decrease in lymphocyte count was found in malignant cases compared to benign cases. Monocyte count did not differ between benign and malignant cases. Derived ratios like NLR, PLR, and MLR were significantly increased in malignant cases, consistent with similar studies [38-41]. Another study found that as breast malignancy stages progressed, haemoglobin, WBC count, and absolute lymphocyte count decreased, while platelet count increased. RBC indices and absolute neutrophil count did not change across stages. NLR and PLR showed a significant increase in Stage-4 compared to other stages (1 to 3). Neutrophil%, lymphocyte%, and MPV were increased in malignant breast cases compared to benign cases. However, there were no significant changes in CBC parameters across the various stages of breast carcinoma, possibly due to a limited number of cases in advanced stages. Other studies have reported increased neutrophils, monocytes, platelet count, and MPV in advanced tumours, along with a decrease in lymphocyte count. The cellular and humoral immune responses play a vital role in limiting cancer initiation and progression by recognising and eliminating them. Higher levels of inflammation cause increased growth factors and cytokines, inducing an angiogenic switch to promote tumour angiogenesis [42]. It has been found that cytokines and inflammatory mediators generate reactive oxygen and nitrogen species, leading to further DNA damage and genomic instability [43], thus exacerbating the situation.

Recently, immune-based therapies have been included in the treatment of cancers. Breast cancer, often considered a "cold" tumour due to its limited ability to induce immune responses, has shown benefits from immune checkpoint inhibitors [44], resulting in improved therapeutic outcomes and long-term survival. Therefore, we can assess the extent of inflammation by monitoring changes in peripheral blood counts.

Limitation(s)

This study has limitations, including its retrospective design and small sample size. Thus, a prospective study with a larger sample size is needed to validate our research findings.

CONCLUSION(S)

The analysis of CBC parameters in breast lesions showed variations in the differential counts of WBC and its derived ratios, such as NLR, PLR, and MLR, in malignant breast diseases. These parameters can be utilised to predict malignant cases early among breast lesions.

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