Association of Hematological Parameters with Nottingham Histologic Grades of Breast Carcinoma in South Indian Population

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aim: To determine the most reliable hematological markers for the prognosis of breast cancer. To evaluate the correlation between hematological parameters and histopathological grading.
Study Design: A retrospective study
Place of Study: This study was carried out in Saveetha Medical College and Hospital, Tamil Nadu, India.
Methodology: Study was started after obtaining the approval from the ethics committee. Histopathological grades 1, 2 and 3 of breast cancer patients were correlated with their hematological parameters.
Results: Out of 104 cases of breast carcinoma, maximum of cases were seen in histopathological grade 2, followed by grade 3 and grade 1 respectively. On correlation with hematological parameters, Hb concentration, RBC count, PCV , MCV , TLC , DLC(neutrophil, lymphocytes) and Absolute lymphocyte count was decreased as the grade increase. RDW increased with higher the grade. Neutrophil lymphocytes ratio showed statistically increased increase in histopathological grade 3 when compared to grade 1.

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Conclusion: Our study showed that the hematological parameters like hemoglobin, RBC count, PCV, WBC count, platelet count, absolute neutrophil count, absolute lymphocyte count, NLR in breast cancer can be a useful guide for disease progression.

1. INTRODUCTION

In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast carcinoma in the past 5 years, making it the world's most prevalent cancer [1,2]. There are more lost disability-adjusted life years by women due to breast cancer globally than any other type of cancer. Breast carcinoma occurs in every country of the world in women at any age most commonly after puberty but with increasing rates in later life. In early-stage breast carcinoma, where the use of systemic therapy has to be determined for every patient, the three main prognostic determinants used in routine clinical practice are lymph node status, tumor size, and histological grade. Histopathological grading when adequately carried out ,provides a simple, inexpensive, and highly accurate method for assessing tumor biological characteristics and patient prognosis [3,4]. Higher tumor grade generally portending a worse prognosis of the patient.

Pathologists assess the grade of breast cancers by using the Nottingham Histologic Score System (the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system), which allows objective scoring of tumors on the basis of three characteristics (Fig. 2) tubule formation or glandular differentiation, nuclear morphology and mitotic activity(4). Tumors are scored on a three-point scale in each of the three categories, and the scores are added for a total of up to nine points. Tumor with a score of 1 for tubule formation have glands in greater than 75% of the tissue and exhibit moderate differentiation, those with a score of 2 have glands in 10%–75% of the tissue, and those with a score of 3 have glands in less than 10% of the parenchyma[5]. Scoring nuclear pleomorphism is arguably the most subjective aspect of the Nottingham system, incorporating features such as nuclear size and prominence of nucleoli. Tumor that are given a score of 1 generally have small regular nuclei with rare nucleoli. Score 2 tumor have larger and mildly pleomorphic nuclei with inconspicuous

nucleoli, and score 3 tumors have markedly enlarged and bizarre nuclear features with prominent nucleoli. Mitotic activity is scored on the basis of a count of mitotic figures in ten high-powered fields; the exact scoring is dependent on microscopic field diameter but follows the principle which are more mitoses are found in higher-grade tumor [6,7] Total scores of 3–5 indicate a low-grade tumor denotes grade 1, while a score of 8–9 corresponds to a high-grade tumor denotes grade 3 with aggressive nature[8]. The effect of peripheral blood counts on prognosis of cancer patients have been studied in several cancer research study. There were some studies in locally advanced breast cancer that showed relationship between disease and hematological parameters. We aimed to determine the relationship between breast carcinoma and these hematological parameters[9-11].

Inclusion criteria:

- Female patients aged more than 20 years with histopathological diagnosed with breast carcinoma.

Exclusion criteria:

- TNM staging is not considered.
- Males with breast carcinoma.
- Pregnant women.
- Patients with benign and inflammatory breast diseases.

2. MATERIALS AND METHODS

A retrospective study was carried out in line with research regulations, including the approval of the Ethical Committee. The study includes 104 patients operated in Saveetha Medical College during the period of January 2017 and December 2020 were divided into three groups as grade1, grade2 and grade 3 according to histopathological grade. In these groups, the preoperative hemoglobin concentration, RBC count, PCV , MCV , MCH , MCHC , RDW, TLC ,

DLC, Absolute neutrophil count, Absolute lymphocytes count and Platelet count were checked using Sysmex Automated Analyzer NX1000. Neutrophil/lymphocyte (N/L) ratios was calculated by dividing Absolute neutrophil count and Absolute lymphocytes count .These results were compared to the grades that emerged from the histopathological results and evaluated for correlation of our study. These hematological parameters were standardized by routine external and internal quality control checks.

3. RESULTS

In the study, out of 61 patients who had been operated between January 2017 and December 2020,On age distribution major of subjects were 45 to 60 years age group. 15 patients were found to be at grade1, 58 patients at grade 2 and 31 patients at grade 3. Patients with grade 2 breast cancer was predominant in this study (Table 1).

Table 1. Histopathological grades and age distribution

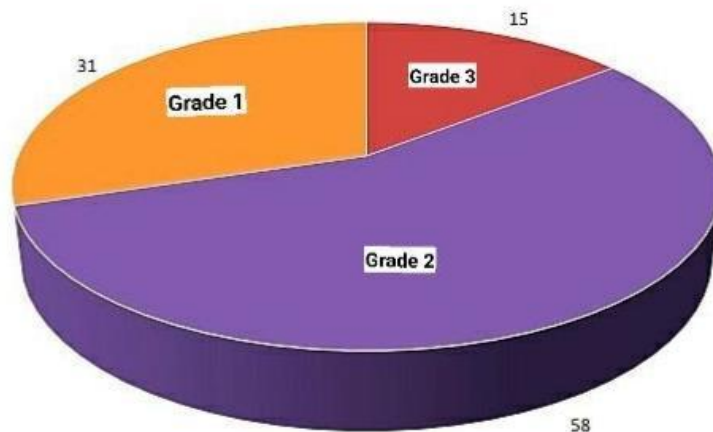| Histopathological grades	Number of cases	Age distribution (Mean ± SD)
Grade 1	15	54.9±12.4
Grade 2	58	50.3±10.5
Grade 3	31	51.0±11.3

Fig. 1. Distribution of patients according to the histopathological grades
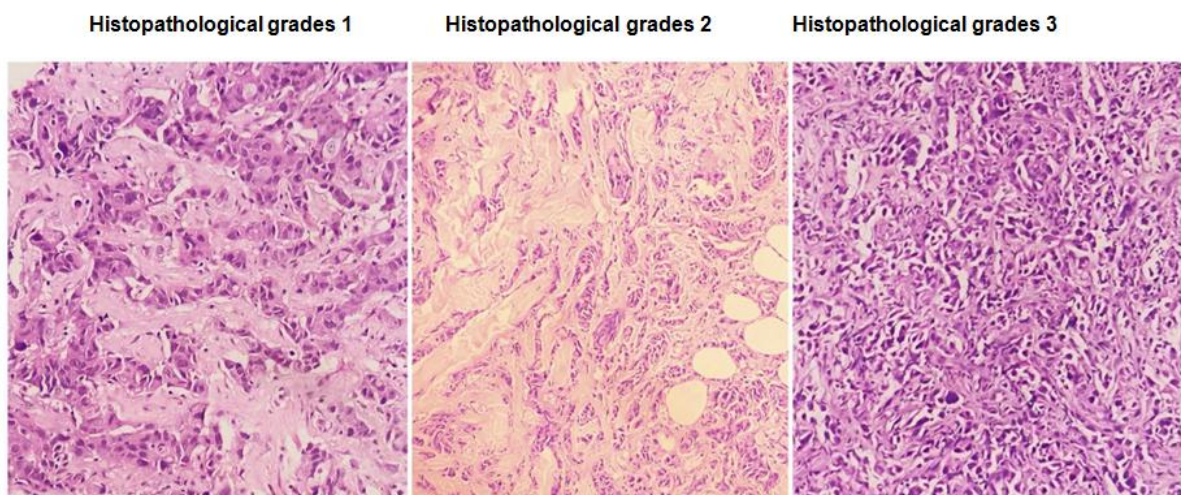

Fig. 2. Histopathological grades of breast carcinoma

Table 2. Comparision of hematological parameters with histopathological grades

Hematological parameters	Histopathological grade-1	Histopathological grade-2	Histopathological grade-3
Hb concentration (g/dl)	12.05 ± 2.95	10.85 ± 2.75	10.55 ± 0.75
RBC (x 10² µl)	3.85 ± 0.83	3.75 ± 1.2	3.47 ± 0.51
Packaged cells volume (%)	34.6 ± 4.7	30.0 ± 6.2	29 ± 3.1
MCV (fL)	82.95 ± 2.95	78.85 ± 15 .85	77.3 ± 15.8
MCH (pg)	25.6 ± 6.3	25.25 ± 5.62	28.7 ± 1.7
MCHC (g/dl)	31.9 ± 0.8	32.15 ± 3.15	32.12 ± 4.15
RDW (%)	12.53 ± 0.72	14.82 ± 3.82	15.3 ± 2.1
Total WBC count (×10³/ul)	8.51 ± 2.7	7.40 ± 1.68	6.22 ± 1.58
Neutrophil (%)	65. 1 ± 14.85	58.6 ± 25.6	51.55 ± 6.45
Lymphocytes (%)	36.5 ± 3.7	25.95 ± 10.5	22.2 ± 11.2
Monocytes (%)	4.75 ± 2.4	6.87 ± 1.3	5.16 ± 2.0
Eosinophils (%)	1.60 ± 2.1	2.25 ± 2.2	2.01 ± 1.7
Basophil (%)	0.04 ± 0.2	0.1 ± 1.4	0.0 ± 0.0
Absolute neutrophil counts	7203 ± 2140	6512 ± 1209	6648 ± 1103
Absolute lymphocytes Counts	3102 ± 1124	2709 ± 822	2231 ± 1039
Platelet counts (×10³/ul)	2.11 ± 0.76	2.09 ± 0.39	2.29 ± 1.8
Neutrophil lymphocytes ratio	2. 9 ± 1.8	4.6 ± 3.1	6.1 ± 1.7

The hemoglobin concentration value among grade1 was 12.05 ± 2.95 , grade 2 was 10.85 ± 2.75 and grade 3 was 10.85 ± 2.75. The red blood cell count value among grade1 was 3.85 ± 0.83 , grade 2 was 3.75 ± 1.2 and grade 3 was 3.47 ± 0.51. Packaged cells volume value among grade1 was 34.6 ± 4.7, grade 2 was 30.0 ± 6.2 and grade 3 was 29 ± 3.1. Hb concentration , RBC count , PCV decreased as grade increase.The mean corpuscular volume value among grade1 was 82.95 ± 2.95, grade 2 was 78.85 ± 15 .85 and grade 3 was 77.3 ± 15.8. PCV and MCV decreased as the grade increase. The mean corpuscular hemoglobin value among grade1 was 25.6 ± 6.3, grade 2 was 25.25 ± 5.62 and grade 3 was 28.7 ± 1.7 The mean corpuscular hemoglobin concentration value among grade 1 was 31.9 ± 0.8, grade 2 was 32.15 ± 3.15 and grade 3 was 32.12 ± 4.15. The red cell distribution width value among grade 1 was 12.53 ± 0.72, grade 2 was14.82 ± 3.82 and grade 3 was 15.3 ± 2.1.RDW increased as the grade increase. On correlation with total leukocyte value among grade 1 was 8.51 ± 2.7, grade 2 was 7.40 ± 1.68 and grade 3 was 6.22 ± 1.58. Neutrophil value among grade 1 was 65.1 ± 14.85, grade 2 was 58.6 ± 25.6 and grade 3 was 51.55 ± 6.45. Lymphocyte value among grade 1 was 36.5 ± 3.7, grade 2 was 25.95 ± 10.5 and grade 3 was 22.2 ± 11.2. Total WBC count, neutrophil, lymphocytes counts decreased as the grade increase. Monocytes value among grade 1 was 4.75 ± 2.4, grade 2 was 6.87 ± 1.3 and grade 3 was 5.16 ± 2.0. Eosinophil value among grade 1 was 1.60 ± 2.1, grade 2 was 2.25 ± 2.2 and grade 3 was 2.01 ± 1.7. Basophil value among grade 1 was 0.04 ± 0.2, grade 2 was 0.1 ± 1.4 and grade 3 was 0.0 ± 0.0. Absolute neutrophil count value among grade 1 was 7203 ± 2140, grade 2 was 6512 ± 1209 and grade 3 was 6648 ± 1103. Absolute lymphocyte count value among grade 1 was 3102 ± 1124, grade 2 was 2709 ± 822 and grade 3 was 2231 ± 1039. ALC deceased as the grade increase. Platelet count value among grade 1 was 2.11 ± 0.76 , grade 2 was 2.09 ± 0.39 and grade 3 was 2.29 ± 1.8. Neutrophil lymphocytes ratio value among grade 1 was 2. 9 ± 1.8 , grade 2 was 4.6 ± 3.1 and grade 3 was 6.1 ± 1.7. NLR deceased as the grade increase (Table 2).

4. DISCUSSION

Hematological parameters are frequently used as a convenient and routine test for the diagnosis of

many diseases, such as anemia, immune dysfunctions, carcinoma and infectious diseases. Breast carcinoma is mostly seen in older women having age above than 45 years, our study revealed that majority of women were aged more than 45 years . According to Binder-Foucard et al., (2013) reported that increase in the age increases the chance of incident of breast carcinoma in women, According to American Cancer Society (2011) the median of breast cancer subjects was observed 61 year during the 2008 to 2012. That indicates breast cancer mostly develops in above than 50 years age. Presence of any type of cancer in family history is high risk of breast cancer especially for blood bond relatives[12]. Variation in hematological parameters in breast carcinoma of different histopathological grades patients may be due to the increase in the levels of pro-inflammatory cytokines including Interlukin-I and Interlukin-6 and Tumor necrosis factor-α. (Liqaa et al., 2014). In our study hemoglobin concentration, red blood cells indices like RBC count, packed cell volume and mean corpuscular volume value decreased as the histopathological grading increased. Ufelle, et al., 2012 reported that the haematocrit values are significantly reduced in pre- and post-surgery of breast cancer patients.

Our study correlated significantly with previous studies which showed decreased hemoglobin concentration .Chronic diseases and cancers can cause decreased production of erythropoietin which in turn leads to decreased production of RBC, resulting in anemia [12,13] The pathogenesis of anemia in breast carcinoma is complex and multi-factorial and, even in the same patient, different mechanisms can prevail at different times (e.g., after surgery or chemotherapy. Anemia can develop as a consequence of malnutrition and malabsorption leading to iron and other nutritional deficiency, e.g., folates and vitamin B12, acute and chronic inflammation, metastatic infiltration of bone marrow, and therapy-related myelosuppression. The widely accepted mechanism is the release of many cytokines such as TNF-α, interferon-δ, and IL-1, IL-6 during carcinogenesis that induces iron retention by the reticuloendothelial system and liver, thereby exerting an inhibitory effect on erythroid precursors[14] . Anemia was associated with decreased survival, decreased tumour response and decreased patient immune system, and directly retracts from patient prognosis On other hand metastasis of cancer cells to bone marrow, leading to suppression of all the hematological parameters. It was also noted that as the histopathological grading increased, all these parameters decreased. Kandemir et al. investigated the prevalence of anemia (Hb conc. <12 g/dl) in 336 women with early stage breast cancer and its association with other known prognostic factors. In our study red cell distribution width was increased as the histopathological grade increase [15]. Similarly study by Seretis et al showed that RDW is a marker of breast cancer activity as a significant high level found in breast cancer compared with breast fibroadenoma[16].

On correlation of white blood cell count with histopathological grades, total leukocyte count, neutrophil count and lymphocytes count decreased as the grade increases. Neutropenia has been shown to be associated with solid tumors especially breast carcinoma. Lyman and Wilmot (2006) and Wolf et al. (2005) found that among patients with solid cancer, breast cancer patients had the highest risk for developing severe neutropenia[16] .There was a decrease in the absolute lymphocyte count in the present study, with an increase in grade of the breast carcinoma especially noted in grade 3. These findings are comparable to studies done by Rana APS et al. and Parkin DM et al, who observed that the decrease in lymphocyte count was proportional to progression of tumor . But , it was in contrast with the Blue Mountains Eye Study cohort of older Australians, where an elevated WBC count was seen with cancer mortality. Nemoto et al and others observed no change in peripheral lymphocyte count in patients of breast carcinoma. The mechanism of tumor immunity is mainly carried out by CD8+ cytotoxic T-cells which mediate killing of tumor cells and which are capable of destroying tumor cells prior to sensitization. Hence, a decrease in these cells causes suppression of tumor immunity and poor prognosis [17]. Higher peripheral blood CD8+ count with higher survival was reported in a study conducted by Lee et al.

On correlation with biomarker , like Neutrophil lymphocyte ratio elevated as grade increases. NLR has a balance between pro-tumor inflammation, anti-tumor immune mechanism and its prognostic significance has been extensively studied but the proper pathogenesis for NLR raise with tumor progression has not been obtained till now. Ozyalvacli et al observed that neutrophil‑to‑lymphocyte ratio was increased in patients with breast cancer compared with patients with benign proliferative breast disease [18]. In addition, Dirican et al and

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Jia et al reported that patients with breast cancer with a low neutrophil‑to‑lymphocyte ratio present longer disease‑free and overall survival times than those who have a high neutrophil‑to‑lymphocyte ratio [19] Similar results have been yielded by several studies , which concluded that patients with a high pre treatment neutrophil-to-lymphocyte ratio have higher 5-year mortality rates than patients with a low pre-treatment neutrophil-to-lymphocyte ratio.

5. CONCLUSION

We conclude there is an association between hematological parameters in different histopathological grade of breast cancer involved in progression and prognosis. The hematological parameters like hemoglobin, RBC count, PCV , WBC count, platelet count, absolute lymphocyte count, NLR in breast cancer can be a useful guide for disease progression. The increase in NLR values can be deleterious to cancer patients as those values are associated with poor prognosis and higher mortality. However further studies with larger sample size from various tertiary care hospitals are required to confirm the findings of the present study. The present study ,aid the treating surgeons to manage the treatment according to the patients condition.

6. LIMITATIONS OF THE STUDY

There were some limitations in our study. Firstly, this was a retrospective study, therefore, complete information was not available for all the patients. So, selection biases cannot be avoided because of the single tertiary hospital-based study. Secondly, the sample size in our study is small and hematological parameters evaluated in this research are transient and susceptible to many factors . Hence, largescale studies involving other Tertiary hospitals are required.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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