European Institute of Knowledge & Innovation

Annals of Innovation in Medicine (AIM) ISSN: 2977-0335

Research Article

Cancer Antigen 15.3 Levels And Lymphocyte To Monocyte Ratio Of Breast Cancer Subjects receiving Chemotherapy In Umuahia, Nigeria

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https://doi.org/10.59652/aim.v3i2.579

Abstract: Cancer Antigen 15.3 level (CA 15.3) is used to monitor response to breast cancer treatment and could also be used to survey disease recurrence after treatment of metastatic breast cancer. Lymphocyte-monocyte ratio (LMR), is a reflection of the hosts immunity and its degree of tumor progression. A low lymphocyte count and a high monocyte count indicates that there's an elevated tumor burden and a poor prognosis for the subject.

Aim of the Study: This study is aimed at finding out the levels of Cancer Antigen 15.3 Level and Lymphocyte to monocyte ratio of breast cancer subjects receiving chemotherapy in Umuahia, Nigeria.

Materials and Methods: A total of 120 subjects were enrolled in this study. They were aged between 14 and 75 years. Of these 120 subjects, 60 were clinically diagnosed breast cancer subjects while 60 were apparently healthy subjects. The age range of BRCA subjects were between 14 and 83, the stage of BRCA were from stage I to IV. The haematological parameters were carried out using the five-part Midray BC-5180 haematology analyzer manufactured by the Chinese Midray company. The determination of the CA15.3 levels was done with an Enzyme linked immunosorbent assay (ELISA) machine. The test kit that was used for this test procedure is AccuBind Elisa microwells CA 15-3.

Results: From this study, at $p<0.05$; there was statistically significant increase in WBC (9.3 ± 4.5 x109/L versus 6.8 ± 1.7x109 /L) (p=0.0001), monocyte (7.4 ± 1.8 % versus 3.3 ± 1.1 %)(<0.0001), mean platelet volume (9.0 ± 1.2 fl versus 8.1 ± 0.7 fl)(<0.0001), and CA 15-3 (23.2 ± 8.0 U/ml versus 9.3 ± 5.4 U/ml)(p=<0.0001) in Breast Cancer Patients when compared with control subjects also, significant statistical decrease was observed in eosinophils (1.5 ± 1.6% versus 2.1 ± 1.9%)(p=0.0413), basophils (0.1 ± 0.2 versus 0.5 ± 0.4)(p=<0.0001), RBC (3.5 ± 0.7 x1012/l versus 4.9 ± 0.6 x1012/l)(p=<0.0001), PCV (27.2 ± 6.4 % versus 35.9 ± 3.0 %)(p= <0.0001), PDW (13.5 ± 0.8 versus 17.0 ± 1.7)(p=<0.0001), HB (8.8 ± 2.1g/dl versus 11.9 ± 1.1g/dl)(p=<0.0001), MPV (9.0 ± 1.2fl versus 8.1 ± 0.7 fl)(p=<0.0001), LMR (4.4 ± 2.5 versus 7.7 ± 6.1)(p= 0.0002), in Breast Cancer Subjects, when compared with control subjects. As CA 15.3 is increased in cancer patients, lymphocyte-monocyte ratio LMR is decreased in cancer patients (r = -0.259(P = 0.046), (r=1.000) (p=0.000).

Conclusion: There was a negative correlation in cancer antigen 15.3 levels and lymphocyte monocyte ratio as the levels of CA 15.3 were increased while LMR levels were reduced. The subjects in this study had better survival outcomes at the 5th chemotherapy session.

Received: April 6, 2025
Accepted: June 10, 2025
Published: June 17, 2025

Keywords: Cancer Antigen 15.3, Lymphocyte to Monocyte Ratio, Breast Cancer, Chemotherapy

1. Introduction

The rapid and unregulated division of abnormal cells leads to a disease called cancer. Accumulation of mutations in tumor or neoplastic cells of the breast is a genetic disease called breast cancer (1). Women suffer this disease mostly and it is the leading cause of cancer related deaths in women in the world (2).

Studies conducted on the prevalence of this disease in Nigeria revealed that annual incidence varies with location and is seen to be higher in urban centers than in rural areas (3) 156 cases were seen in Maiduguri (4), 116 cases in Ibadan (5), 57 cases in Ilorin (5), and 16 cases in Calabar (3) and the ratio of men to women having this disease is about 1:126 of the entire population which could be as a result of females having more estrogen and progesterone that promote breast growth (6). From several researches carried out, it has been observed that there's a strong association between inflammation and cancer (7). Hence, the importance of the cells involved in inflammatory responses like the lymphocytes, monocytes and neutrophils (8). Therefore, these three cell lines are regarded as prognostic factors in various cancers (8). Lymphocytes for example are very important in host tumor immunity and are also involved in cytotoxic cell death and inhibition of tumor cell proliferation and migration (14).

When there's a reduction in the total lymphocyte count, there will be an insufficient immunologic reaction to the tumor hence, progression and metastasis of the tumor will be promoted (9). Monocytes on the other hand, are known to infiltrate tumors and differentiate into tumor-associated macrophages (10). These tumor-associated macrophages are involved in tumor proliferation, invasion, metastasis, neovascularization and reoccurrence (15).

Therefore, an increased monocyte count reflects high tumor proliferation in cancer patients (15). Lymphocyte-monocyte ratio (LMR), is therefore a reflection of the hosts immunity and its degree of tumor progression (11). Therefore, a low lymphocyte counts and a high monocyte count indicates that there's an elevated tumor burden and a poor prognosis for the patient (11).

Cancer antigen 15.3 is a heterogeneous 300KD glygoprotein made by breast cancer cells (12). It was discovered with the use of two monoclonal antibodies 115D8 and DF3 that were raised against breast carcinoma cells (12). This test is specific for breast malignancies (12). It appears in higher concentration and has been found to have a higher incidence in breast cancer compared to other cancers. It is used to monitor response to breast cancer treatment and the recurrence of the disease. CA 15-3 levels are mostly recommended for patients with metastatic breast cancer that are undergoing treatment therapy to monitor their tumor and check if the tumor is responding to the treatment therapy (12). It could also be used to survey disease recurrence after treatment of metastatic breast cancer.

An increase in CA15-3 levels could indicate that the treatment failed while a decrease in the levels indicate that the tumor is responding to the treatment (16). Reference ranges are usually less than 30U/ml. According to a retrospective study by (16), it was observed that in 62% of the breast cancer patients who were treated for early breast cancer, levels of CA15-3 found in them were above 30U/ml as at the time metastasis was discovered. Some benign causes of elevated CA15-3 include; Chronic hepatitis, liver cirrhosis, tuberculosis, benign breast diseases, pelvic inflammatory disease, lactation and pregnancy (16).

2. Aim of the study

This study was aimed at evaluating the cancer antigen 15.3 levels and lymphocyte to monocyte ratio of breast cancer subjects receiving chemotherapy in Umuahia, Nigeria.

2.1 Study design

A case-control study design was used in this study. Test Samples were obtained from patients actively suffering from breast cancer which was confirmed by clinical presentations. Subjects who presented with nipple discharge, pain in one or both breasts, nipple/skin retraction or swelling in the armpit, whose biopsies were sent for histology by the oncology consultants and were confirmed cancerous by the histology studies, were selected as the test subjects in this study and the control samples were obtained from apparently healthy subjects.

2.2 Study area

This study was carried out in Federal Medical Center Umuahia. Umuahia being the capital city of Abia state and one of the thirty-six states of Nigeria. It is located between latitude 4˚49.30'N - 6˚02'N and between long 7˚08'E - 8° 04'E in the southeastern part of Nigeria (Igbokwe and Nwankwo, 2011).

2.3 Sample collection

5ml of venous blood samples was obtained and 3mls was put in an Ethylene diamine tetracetic acid (EDTA) bottle while the other 2mls was put in a plain bottle so that the serum will be extracted.

2.4 Sample analysis

The haematological parameters were carried out using the five-part Midray BC-5180 haematology analyzer manufactured by the Chinese Midray company. The determination of the CA15.3 levels was done with an Enzyme linked immunosorbent assay (ELISA) machine.

2.5 Data analysis

Data were analyzed using Graph pad Prism version 8.2 and descriptive statistics for mean and standard deviation. Inferential statistics for students t-test, ANOVA and correlation.

3.0 Results

This study was carried out to evaluate the cancer antigen 15.3 levels and lymphocyte to monocyte ratio of breast cancer subjects receiving chemotherapy in Umuahia, Nigeria.

Table 1: Demographic Characteristics of Study participants

Parameter	Frequency	Percentage (%)
Total No.	120	100.00
BRCA Subjects	60	50
Control Subjects	60	50
Age Range (BRCA subjects in years)		
14-23	4	6.67
24-33	10	16.67
34-43	26	43.33
44-53	12	20

54-63	4	6.67
64-73	2	3.33
74-83	2	3.33
Chemo Stopped period	15	25
Period ended naturally	10	16.67
Still seeing period	35	58.33

There was statistically a linear significant increase in percentage neutrophils from the 6th chemotherapy session 0-2 doses (54.1±9.2), 3-5 doses (54.7±14.1), 6-8 doses (61.6± 11.6), >8 doses (66.4±10.2). Percentage lymphocyte indicated statistically significant decrease in patients receiving chemotherapy above eight sessions 0-2 doses (35.8± 10.4), 3-5 doses (35.9 ± 14.1), 6-8 doses (29.6± 10.5), >8 doses (23.6± 9.5). Mean cell haemoglobin concentration of breast cancer subjects indicated statistically significant decrease only after more than eight sessions of chemotherapy 0-2 doses (32.4±0.6), 3-5 doses (33.3 ±0.8), 6-8 doses (32.8± 1.0) >8 doses (32.2±1.3). Mean platelet volume showed linear statistically significant increase that peaked from the ninth session of chemotherapy 0-2 doses (8.1 ± 1.2), 3-5 doses (8.9 ± 1.1), 6-8 doses (9.1 ± 1.0), >8 doses (9.5± 1.0). Lymphocyte to monocyte ratio indicated statistically declining values 0-2 doses (5.5± 2.3), 3-5 doses (5.7±3.6), 6-8 doses (3.5± 1.5), >8 doses (3.2±1.4) , while CA-15.3 showed fluctuating values with sharp significant decrease at the third to fifth session of chemotherapy 0-2 doses (25.0± 7.5), 3-5 doses (18.7 ±6.1), 6-8 doses (61.6 ± 11.6), >8 doses (66.4 ± 10.2). Other parameters like WBC, eosinophils, monocytes, basophils, RBC, HB, PCV, MCH, MCV, platelets and PDW indicated no statistically significant difference. Details are shown in table 2 below;

Table 2: Comparison of Mean and Standard Deviation of Haematological Parameters and Cancer Antigen 15.3 in Breast Cancer Subjects based on Chemotherapy Dose

Parameters (Units)	0-2 Doses (a); n = 14 $\bar{x} \pm SD$	3-5 Doses (b); n = 14 $\bar{x} \pm SD$	6-8 Doses (c); n = 13 $\bar{x} \pm SD$	>8 Doses (d); n = 19 $\bar{x} \pm SD$	F-value	p-value	TMC
WBC ($x10^9$)	6.7 ± 2.0	10.4 ± 4.6	9.1 ± 4.7	10.5 ± 5.1	2.371	0.0801^{NS}	
Neutrophils (%)	54.1 ± 9.2	54.7 ± 14.1	61.6 ± 11.6	66.4 ± 10.2	4.409	0.0075^{S}	a-d 0.0160 b-d 0.0238
Lymphocytes (%)	35.8 ± 10.4	35.9 ± 14.1	29.6 ± 10.5	23.6 ± 9.5	4.343	0.0080^{S}	a-d 0.0196 b-d 0.0181
Eosinophils (%)	1.8 ± 1.7	1.2 ± 1.9	1.0 ± 0.8	1.8 ± 1.6	0.849	0.4727^{NS}	
Monocytes (%)	6.8 ± 1.4	7.1 ± 1.8	7.6 ± 1.8	7.9 ± 2.0	0.967	0.4147^{NS}	
Basophils (%)	0.2 ± 0.1	0.2 ± 0.5	0.1 ± 0.1	0.1 ± 0.1	1.361	0.2640^{NS}	
RBC ($x10^{12}$)	3.8 ± 0.8	3.4 ± 0.7	3.6 ± 0.6	3.3 ± 0.7	1.086	0.3625^{NS}	
HB (g/dl)	9.3 ± 2.1	8.8 ± 2.1	9.1 ± 1.7	8.4 ± 2.2	0.640	0.5925^{NS}	
PCV (%)	28.7 ± 6.7	26.8 ± 6.7	27.8 ± 5.0	26.0 ± 6.9	0.519	0.6707^{NS}	
MCV (fl)	75.1 ± 7.8	76.8 ± 6.0	75.3 ± 5.9	76.1 ± 7.9	0.158	0.9241^{NS}	
MCH (pg)	24.4 ± 2.5	25.9 ± 2.8	25.3 ± 2.1	24.6 ± 2.5	1.037	0.3831^{NS}	
MCHC (g/dl)	32.4 ± 0.6	33.3 ± 0.8	32.8 ± 1.0	32.2 ± 1.3	3.133	0.0326^{S}	b-d 0.0264
Platelets ($x10^9$)	298.6 ± 70	269.7 ± 73	264.1 ± 55	277.9 ± 63	0.722	0.5427^{NS}	
PDW (fL)	13.3 ± 0.9	13.2 ± 1.0	13.6 ± 0.9	13.7 ± 0.6	1.080	0.3651^{NS}	
MPV (fL)	8.1 ± 1.2	8.9 ± 1.1	9.1 ± 1.0	9.5 ± 1.0	4.295	0.0085^{S}	a-d 0.0040
LMR	5.5 ± 2.3	5.7 ± 3.6	3.5 ± 1.5	3.2 ± 1.4	4.514	0.0066^{S}	a-d 0.0392

							b-d 0.0223
CA 15.3	25.0 ± 7.5	18.7 ± 6.1	21.8 ± 8.1	26.2 ± 8.4	2.914	0.0422S	b-d 0.0390

Key: BRCA = Breast Cancer; $\bar{x}$ = Mean; SD = Standard Deviation; S = Significant; NS = Non-Significant; LMR = Lymphocyte to Monocyte Ratio; RBC = Red Blood Cell Count; HB = Haemoglobin Concentration; PCV = Packed Cell Volume; MCV = Mean Cell Volume; MCH = Mean Cell Haemoglobin; MCHC = Mean Cell Haemoglobin Concentration; PDW = Platelet Distribution Width; MPV = Mean Platelet Volume; CA 15.3 = Cancer Antigen 15.3; TMC = Tukey Multiple Comparison Test.

Table 3: Correlation Matrix of the Parameters that showed Statistical Significance

	CA 15.3	WBC	EOS	MONO	BASO	RBC	HB	PCV	PDW	MPV	LMR
CA 15.3	r = 1.000	0.050	0.153	0.154	-0.019	0.082	0.065	0.097	0.240	-0.104	-0.259
	p = 0.000	0.681	0.244	0.241	0.883	0.532	0.621	0.463	0.065	0.429	0.046
WBC	r = 0.054	1.000	-0.138	0.255	0.196	-0.012	0.081	0.105	-0.193	0.007	-0.309
	p= 0.681	0.000	0.295	0.049	0.133	0.927	0.538	0.425	0.140	0.957	0.016
Eosinophils	r = 0.153	-0.130	1.000	0.089	-0.028	-0.088	-0.103	-0.087	0.048	0.082	-0.063
	p = 0.244	0.295	0.000	0.496	0.833	0.502	0.433	0.510	0.713	0.531	0.635
Monocyte	r = 0.154	0.255	0.089	1.000	0.154	-0.140	-0.084	-0.077	0.096	0.181	-0.644
	p = 0.241	0.049	0.496	0.000	0.239	0.286	0.523	0.558	0.467	0.165	0.008
Basophil	r = -0.019	0.196	-0.028	0.154	1.000	-0.040	-0.002	0.021	0.122	-0.004	-0.132
	p = 0.883	0.133	0.833	0.239	0.000	0.763	0.986	0.873	0.354	0.973	0.314
RBC	r = 0.082	-0.01	-0.088	-0.140	-0.040	1.000	0.922	0.922	-0.121	0.032	0.385
	p = 0.532	0.927	0.502	0.286	0.763	0.000	0.026	0.026	0.356	0.810	0.002
HB	r = 0.065	0.081	-0.103	-0.084	-0.002	0.922	1.000	0.987	-0.073	0.057	0.296
	p = 0.621	0.538	0.433	0.523	0.986	0.026	0.000	0.048	0.577	0.666	0.022
PCV	r = 0.097	0.105	-0.087	-0.077	0.021	0.922	0.987	1.000	-0.074	0.038	0.304
	p = 0.463	0.425	0.510	0.558	0.873	0.026	0.048	0.000	0.575	0.775	0.018
PDW	r = 0.240	-0.19	0.048	0.096	0.122	-0.121	-0.073	-0.074	1.000	0.491	-0.111
	p = 0.065	0.140	0.713	0.467	0.354	0.356	0.577	0.575	0.000	0.005	0.396
MPV	r = -0.104	0.007	0.082	0.181	-0.004	0.032	0.057	0.038	0.491	1.000	-0.064
	p = 0.429	0.957	0.531	0.165	0.973	0.s810	0.666	0.775	0.005	0.000	0.628
LMR	r = -0.259	-0.30	-0.063	-0.644	-0.132	0.385	0.296	0.304	-0.111	-0.064	1.000
	P = 0.046	0.016	0.635	0.008	0.314	0.002	0.022	0.018	0.396	0.628	0.000

Key: p = correlation p-values; r = Pearson correlation; Blue = indicates correlations with statistical significance

4.0 Discussion

There was statistically a linear significant increase in percentage neutrophils from the 6th chemotherapy session. Percentage lymphocyte indicated statistically significant decrease in patients receiving chemotherapy above eight sessions. Mean cell haemoglobin concentration of cancer patients indicated statistically significant decrease only after more than eight sessions of chemotherapy, reduction in haemogloblin levels in the breast cancer subjects after chemotherapy. Mean platelet volume showed linear significant increase that peaked from the ninth session of chemotherapy. Lymphocyte to monocyte ratio indicated declining values, while CA-15.3 showed fluctuating values with sharp significant decrease at the third to fifth session of chemotherapy.

4.1 Conclusion

There was a negative correlation between Cancer Antigen (CA15-3) and lymphocyte to monocyte ratio as the levels of cancer antigen 15.3 were increasing, the levels of lymphocyte to monocyte ratio were reducing.

4.2 Recommendation

It is therefore recommended that:

a. Chemotherapy should be used under strict medical observation because from this study, at the 6th chemotherapy session, neutrophil counts were still at high levels which indicates poor prognosis for the subjects.

b. Care should be taken not to exceed the 5th cycle of chemotherapy because at the 5th cycle of chemotherapy in this study, subjects had better survival outcomes when compared to subjects at above 6 chemotherapy cycles.

4.3 Contribution to knowledge

a. Subjects in this study had better survival outcomes at the 5th chemotherapy session.

b. As cancer antigen (CA 15.3) level is increased in cancer patients, lymphocyte-monocyte ratio (LMR) is decreased in breast cancer patients in this study.

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