Original Article

Utilizing peripheral blood inflammatory biomarker (PBIB) to predict response to systemic therapy in patients with breast cancer

Atlal Abusanad

Department of Internal Medicine, Medical Oncology Division, Faculty of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

Abstract

Background: Inflammation is a recognized factor in cancer progression and resistance to treatments. Several studies correlated inflammation-related peripheral blood inflammatory biomarkers (PBIB) to disease progression and poor survival in various cancer types and different populations. Nonetheless, inflammation is affected by the distinctive characteristics and environmental exposure of each population. There is no prior study addressing the association of pre-treatment inflammatory markers with outcomes in patients with breast cancer (BC) from Saudi Arabia. In this study, we evaluated the prognosis of locally advanced breast cancer (LABC) in relation to several PBIB. **Materials and Methods:** We retrospectively analyzed the data of female patients with LABC undergoing neoadjuvant chemotherapy (NACT). Demographics, body mass index (BMI), clinicopathologic characteristics and stage of the tumor, follow-up status, and response to treatment were collected. Outcomes were evaluated in relation to pre-treatment peripheral blood indices that were grouped based on the local laboratory cutoff values. Objective response rate (ORR) was predefined and assessed according to the post-NACT magnetic resonance imaging (MRI) breast and subcategorized into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). **Results:** A total of 172 female patients with BC met the eligibility criteria from January 2014 to December 2019. The mean age at diagnosis was 53.4 ± 11, and BMI was 31.2 ± 6. Left BC accounted for 54.7%, and the majority was invasive ductal carcinoma (85.5%), moderately differentiated (51%), stage III (AJCC 8th edition) (73%), and estrogen receptor (ER)-positive tumor (79.1%). Human epidermal growth factor receptor 2 (HER2)-positive BC was reported in 32% and triple-negative breast cancer (TNBC) in 10%. Radiologic CR accounted for the majority of ORR (71.5%). Higher percentage of patients with normal red cell distribution width (RDW) of red blood cell (RBC) and low neutrophil–lymphocyte ratio (NLR) had CR with a significant *P* value of 0.003 and 0.014, respectively. **Conclusion:** Among several peripheral blood indices, RDW and NLR significantly influenced ORR. They can be explored further to potentially predict response after systemic therapy in patients with LABC. The great advantage of these biomarkers stems from their availability and affordability in routine clinical practice.

Keywords: Breast cancer, complete response, inflammation, neoadjuvant chemotherapy, neutrophile–lymphocyte ratio, peripheral blood

Introduction

Breast cancer (BC) is the most common malignancy in women and the second most common cancer overall. It was diagnosed in approximately 2 million people in 2018.[1] It is the most prevalent malignancy among Saudi women where 29% of females of all ages with cancer were diagnosed with BC in 2020.[2] According to a recent survey of cancer-related mortality among Saudi women,

Address for correspondence: Dr. Atlal Abusanad, Department of Internal Medicine, Medical Oncology Division, Faculty of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.
E-mail: atlal.abusanad@gmail.com

Received: 10-07-2023 **Revised:** 31-08-2023
Accepted: 11-09-2023 **Published:** 21-12-2023

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1125_23

How to cite this article: Abusanad A. Utilizing peripheral blood inflammatory biomarker (PBIB) to predict response to systemic therapy in patients with breast cancer. J Family Med Prim Care 2023;12:3368-73.

BC is the ninth leading cause of death among Saudi women.[3] It is anticipated that BC rates in Saudi Arabia will rise in the future due to population expansion and aging.[4]

In addition to the fact that cancer has a genetic basis in its development, several studies have shown that inflammation plays a role in the progression and spread of cancer.[5,6] A relationship between the level of particular inflammatory markers (e.g., peripheral blood neutrophils, lymphocytes, monocytes, and platelets) and different malignancies was demonstrated. Elevated neutrophils and platelets in peripheral blood have been linked to a lower risk of death in patients with cancer.[7] Likewise, elevated monocyte count was associated with poor outcomes and progression-free survival,[8] while a high lymphocytic count was linked to a favorable prognosis, and a low lymphocyte count was linked to a higher cancer mortality rate.[9] Therefore, peripheral blood inflammatory biomarker (PBIB) such as the neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio (LMR), and platelet–lymphocyte ratio (PLR) can be utilized as measures of the host immunological status to predict cancer-related outcomes.[10] A meta-analysis and systematic review revealed that NLR plays a prognostic function in BC, as it was associated with overall survival (OS) and disease-free survival (DFS).[11] A similar study found that higher PLR was associated with poor outcome in patients with BC.[12] Furthermore, NLR and PLR have been shown to influence the probability of death in patients with BC.[13] Low LMR also has been linked to a poor DFS rate in triple-negative breast cancer (TNBC).[14] Platelet activation plays a role in the progression and spread of cancer. Mean platelet volume (MPV) estimates the mean size of platelets in peripheral blood, which is then used to evaluate platelet activation.[15]

Several studies have shown that pre-treatment PBIB can be used to predict response to neoadjuvant chemotherapy (NACT) in BC. A high pre-treatment NLR was associated with increased mortality in a cohort of 437 women with BC, which was described as a significant risk factor for mortality regardless of chemotherapy regimen.[16] Furthermore, a low pre-treatment LMR was related to a superior NACT effect in patients with BC. Hence, the measurement of pre-treatment PBIB can be utilized to predict outcomes and response to treatment. Hospitalists, family medicine, and primary care practitioners are frequently involved in community-based oncology practices, which can greatly benefit from the use of inexpensive blood tests that are easily accessible.[17] With the use of teleoncology, the coronavirus disease 2019 (COVID-19) epidemic has essentially moved the focus of care to a local provider, where a pre-set treatment plan may be put together by a specialized multidisciplinary team and conducted by a local community practice team, aiming for prompt and high-quality care.[18] The community practice team can closely monitor patients receiving treatment with the use of these blood biomarkers, identify those who are less likely to exhibit a favorable response to chemotherapy, and decide whether to refer them to a higher oncology center.

Each population has distinctive traits and environmental exposures that influence inflammation differently. Therefore, a population-specific assessment of the relationship between inflammation and cancer outcomes is needed. There has been no prior research into the relationship of pre-treatment inflammatory markers with outcomes in Saudi patients with BC. In this study, we assessed the response of locally advanced breast cancer (LABC) to NACT in relation to various PBIB.

Materials and Methods

A total of 172 individuals with a histopathologically confirmed BC diagnosis were included in this retrospective cohort between January 2014 and December 2020 from King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Data on their medical history, height, weight, body mass index (BMI), pathological and laboratory findings, and post-therapy radiological evaluation were collected. The project was approved by the Biomedical Ethics Committee. All clinical data were anonymized to ensure patient privacy. Patients with metastatic BC, those who lost follow-up, those who lacked pathological or laboratory information, and those who had a history of systemic inflammatory or chronic conditions including systemic lupus erythematosus, hematological illness, or bone marrow disease before treatment were excluded.

Tumor location, size, histological grade, lymph node status, metastasis (lung, brain, and bone), hormone receptor status, and human epidermal growth factor receptor 2 (HER2) status were all collected.

Based on post-therapy radiological examination by mammography and breast magnetic resonance imaging (MRI) ± computed tomography (CT) chest abdomen and pelvis, response status was divided into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Based on radiological tests and consultant notes, patient follow-ups were recorded, and the last follow-up status was determined appropriately. To calculate the inflammatory indices (NLR, LMR, and PLR), baseline counts of neutrophils, lymphocytes, monocytes, and platelets in peripheral blood were recorded.

NLR, LMR, and PLR cutoff values were obtained from a comparable study that employed a ratio of 3%, 6.2%, and 135%, respectively.[13,16] For red cell distribution width (RDW), a reference range from a previous research on BC (11-14.1) was used.[19] The data were input into a secure Excel spreadsheet and analyzed using the Statistical Package for Social Sciences (SPSS) version 21. To investigate the relationship between inflammatory parameters and responder status, an association analysis and a Chi-square test were used. A *P* value of 0.05 was regarded as significant.

Results

A total of 172 female patients with BC met the eligibility criteria from January 2014 to December 2019. The mean age

at diagnosis was 53.4 ± 11, and BMI was 31.2 ± 6. Left BC accounted for 54.7**%,** and the majority was invasive ductal carcinoma (85.5%), moderately differentiated (51.2%), stage III (AJCC 8th edition) (73%), estrogen receptor (ER)-positive tumor (79.1%). HER2-positive BC was reported in 32% and TNBC in 10% [Table 1]. Post-treatment progression and metastasis occurred in six patients (3.5%).

The majority of post-treatment responses were CR in 123 (71.5%) patients, followed by SD, while PD is reported as the least type of response (3.5%). Follow-up status was documented with most of the patients alive with CR in 106 (61.6%) patients [Table 2]. Less than 20% of the patients lost follow-up or were reported as deceased.

Higher percentage of patients with normal RDW of red blood cell (RBC) and low NLR had CR with a significant *P* value of 0.003 and 0.014, respectively. All other parameters showed a non-significant *P* value. Most of the patients in our study had normal RDW (84.9%). However, NLR in the majority was low (84.3%). The level of both LMR and PLR whether high or low did not influence the type of response to treatment as shown in Table 3.

Table 1: Clinical and pathological characteristics

	n	%
Pathological type		
Ductal	147	85.5
Lobular	21	12.2
Mixed	4	2.3
Histological grade		
G1	29	16.9
G2	88	51.2
G3	53	30.8
Unknown	2	1.2
Tumor origin		
Right breast	77	44.8
Left breast	94	54.7
Unknown	1	0.6
ER mutation		
Positive	136	79.1
Negative	31	18
Unknown	5	2.9
PR mutations		
Positive	117	68
Negative	49	28.5
Unknown	6	3.5
HER2 mutation		
Positive	55	32
Negative	107	62.2
Unknown	10	5.8
Total	172	100
n	**Mean**	**Std. deviation**
Age (years)		
172	53.4	11
BMI		
172	31.2	6

G1 (well-differentiated), G2 (moderately differentiated), G3 (poorly differentiated)

Table 2: Neoadjuvant chemotherapy response and last follow-up status

	n	%
Complete response (CR)	123	71.5
Type of response		
Partial response (PR)	20	11.6
No change or stable disease (SD)	23	13.4
Progressive disease (PD)	6	3.5
Status of Last FU		
Alive with CR	106	61.6
Alive with PR	9	5.2
Alive with SD	17	9.9
Alive with PD	8	4.7
Lost FU or deceased	32	18.6
Total	172	100

*CR (complete disappearance of the tumor in the imaging or complete response), PR (partial response >30% but no CR), SD (no change or <25% increase or decrease in tumor size in the absence of new lesions), PD (>25% increase in tumor size and/or new lesion)

Discussion

BC is the most common cancer in women and the second most common cancer in the general population. Similarly, it is a common malignancy among Saudi females, with an incidence of 29% in 2020.[1,2]

NACT is a well-established treatment option for patients with LABC. Despite surgical and chemotherapeutic therapies, about 30% of patients with negative axillary lymph nodes and 50% of patients with positive axillary lymph nodes relapse within five years.[20] Traditionally, tumor size, lymph node metastasis, clinical stage, pathological grade, and molecular subtype have all been identified as independent prognostic factors in BC. Other factors play a role in the prognosis of BC such as the host immune response, which is manifested by inflammatory processes triggered by malignant cells, has lately been recognized, and it may influence cancer patient outcomes.[21,22]

This inflammatory response is manifested by white cell differentials (i.e., neutrophils, lymphocytes, platelets, and monocytes) and their ratios (e.g., NLR, PLR, and LMR), which are regularly measured in clinical practice for patients before, during, and after treatment. Measuring these parameters may be beneficial in evaluating patients throughout therapy and follow-up to optimize outcomes.[23-25]

On a biological level, the inflammatory response induced by tumor cells causes alterations in circulating white blood cells (WBCs) such as neutrophilia due to increased cytokines, which stimulate bone marrow to produce neutrophils. These immune response modifications can enhance tumor growth and progression by functioning as a pro-metastatic factor.[26] Similarly, cancer-induced lymphocytopenia has been linked to tumor burden, paraneoplastic inflammatory syndrome, metastatic locations, and a lower survival rate.[27] Furthermore, chronic inflammation influences carcinogenesis by generating reactive

Table 3: Association of inflammatory biomarkers and response to neoadjuvant chemotherapy

Variables (*n*=172)	CR (*n*=123) *n* (%)	PR (*n*=20) *n* (%)	SD (*n*=23) *n* (%)	PD (*n*=6) *n* (%)	*P*
NLR					
High >3	22 (17.9%)	2 (10%)	0 (0%)	3 (50%)	0.014
Low ≤3	101 (82.1%)	18 (90%)	23 (100%)	3 (50%)	
RDW					
High >14.1	22 (17.9%)	2 (10%)	0 (0%)	0 (0%)	0.003
Normal 11-14.1	100 (81.3%)	18 (90%)	23 (100%)	5 (83.3%)	
Low <11	1 (0.8%)	0 (0%)	0 (0%)	1 (16.7%)	
LMR					
High >6.2	15 (12.2%)	4 (20%)	2 (8.7%)	2 (30%)	0.673
Low ≤6.2	108 (87.8%)	16 (80%)	21 (91.3%)	4 (80%)	
PLR					
High >135	69 (56.1%)	10 (50%)	9 (39.1%)	3 (50%)	0.504
Low ≤135	54 (43.9%)	10 (50%)	14 (60.9%)	3 (50%)	

oxygen and nitrogen radicals, thus propagating deoxyribonucleic acid (DNA) alterations in the host. In patients with cancer, the body's response to this process may result in a negative outcome by affecting normal cellular integrity, causing additional degradation and abnormal cellular proliferation.[6,28]

This study investigated the clinical value of pre-treatment PBIB (PLR, NLR, LMR, RDW, and MPV) as predictive makers of response to NACT in LABC. NLR is an index reflecting immunological and inflammatory responses that has been studied in several malignancies. The increase or decrease in NLR indicates a change in neutrophils or lymphocyte count. The high ratio reveals a decrease in lymphocyte count or an increase in neutrophil count relative to normal patients.[13] Neutrophils are the primary source of circulating angiogenetic and growth factors that contribute to tumor growth and progression. Lymphocytes, however, have a protective host response that includes cytotoxic cell death and the generation of cytokines that suppress tumor cell development.[14-16]

Low NLR was associated with CR (71.5%) after NACT in our study, indicating a potential predictor of better outcome and prognosis in patients with BC. Another study suggested that a high NLR is associated with a worse prognosis in patients with BC.[11] High RDW has been linked to a variety of cardiovascular, rheumatological, and inflammatory disease outcomes. It has also been related to the production of circulating cytokines, which contributes to the progression of inflammation.[29,30] High RDW has been associated with a worse prognosis in patients with cancer, indicating increased disease activity and progression. RDW could be used as a potential pre-treatment predictor of response in patients with BC and other malignancies.[31,32]

These values can be maintained within normal ranges by optimizing the patient's health status before treatment, as well as treating other comorbidities that can alter these parameters and contribute to cancer progression, poor prognosis, and survival. Family physician and primary care practitioner have a major role in optimizing the patient's health through managing chronic illness, comorbidities, and polypharmacy. Moreover, hospitalists, family medicine, and primary care practitioners are frequently involved in community-based oncology practices,[17] which can greatly benefit from the use of inexpensive blood tests that are easily accessible. Patients from rural areas with limited access to timely cancer care can benefit the most where a pre-set treatment plan can be put together by a multidisciplinary team from a specialized oncology center and conducted by a local community practice team, aiming for prompt and high-quality care. The COVID-19 epidemic has shifted the focus of care to a local practice through the utilization of teleoncology.[18] Therefore, the community practice team can closely monitor patients receiving treatment with the use of these blood biomarkers, identify those who are less likely to exhibit a favorable response to chemotherapy, and decide whether to refer them to the specialized oncology center.

Individualized considerations for patients with cancer based on their baseline PBIB, in addition to other tumor features before therapy, can play an important role during treatment. In addition, examining NLR patterns and variations over time may help to determine recurrence, resulting in earlier detection, intervention, and improved outcomes. Drugs that interfere with neutrophil functions such as reparixin CXCR1 and CXCR2 inhibitors with suppression of the inflammatory reaction could be used in combination with chemotherapeutic regimens to optimize outcomes as proposed by Ref.[33]

This study has some limitations, including that data came from a single site, some OS data were missing, and some patients' follow-up times were lost. Furthermore, the level of inflammatory biomarkers in the peripheral blood may have been confounded by unidentified patient's factors.

Conclusions

PBIB predict therapy response in patients with BC. RDW and NLR were two peripheral blood indices that predicted response to NACT in patients with BC. The availability and affordability of these biomarkers in routine clinical practice is are a significant advantage.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. doi: 10.3322/caac.21660.
2. Cancer incidence report in Kingdom of Saudi Arabia 2020. Available from: https://shc.gov.sa/Arabic/NCC/Activities/AnnualReports/Cancer%20Incidence%20Report%202020.pdf.
3. World Health Organization, International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today/data/factsheets/populations/682-saudi-arabia-fact-sheets.pdf.
4. Abusanad A, Alghamdi M, Bakkar M, Jazieh AR. General oncology care in the kingdom of Saudi Arabia. In: Al-Shamsi HO, Abu-Gheida IH, Iqbal F, Al-Awadhi A. (eds) Cancer in the Arab World. Springer, Singapore; 2022. doi: 10.1007/978-981-16-7945-2_14.
5. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, *et al.* Inflammation and tumor progression: Signaling pathways and targeted intervention. Signal Transduct Target Ther 2021;6:263. doi: 10.1038/s41392-021-00658-5.
6. Greten FR, Grivennikov SI. Inflammation and cancer: Triggers, mechanisms, and consequences. Immunity 2019;51:27-41. doi: 10.1016/j.immuni.2019.06.025.
7. Schmidt H, Suciu S, Punt CJ, Gore M, Kruit W, Patel P, *et al.* Pretreatment levels of peripheral neutrophils and leukocytes as independent predictors of overall survival in patients with American joint committee on cancer stage IV Melanoma: Results of the EORTC 18951 biochemotherapy trial. J Clin Oncol 2007;25:1562-9. doi: 10.1200/JCO.2006.09.0274.
8. Jiang Y, Xu D, Song H, Qiu B, Tian D, Li Z, *et al.* Inflammation and nutrition-based biomarkers in the prognosis of oesophageal cancer: A systematic review and meta-analysis. BMJ Open 2021;11:e048324. doi: 10.1136/bmjopen-2020-048324.
9. Papaioannou E, Sakellakis M, Melachrinou M, Tzoracoleftherakis E, Kalofonos H, Kourea E. A standardized evaluation method for FOXP3+tregs and CD8+T-cells in breast carcinoma: Association with breast carcinoma subtypes, stage and prognosis. Anticancer Res 2019;39:1217-32. doi: 10.21873/anticanres.13232.
10. Yang J, Guo X, Wu T, Niu K, Ma X. Prognostic significance of inflammation-based indexes in patients with stage III/IV colorectal cancer after adjuvant chemoradiotherapy. Medicine (Baltimore) 2019;98:e14420. doi: 10.1097/MD.0000000000014420.
11. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: A systematic review and meta-analysis. Breast Cancer Res 2017;19:2. doi: 10.1186/s13058-016-0794-1.
12. Zhu Y, Si W, Sun Q, Qin B, Zhao W, Yang J. Platelet-lymphocyte ratio acts as an indicator of poor prognosis in patients with breast cancer. Oncotarget 2017;8:1023-30. doi: 10.18632/oncotarget.13714.
13. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, *et al.* Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer 2015;113:150-8. doi: 10.1038/bjc.2015.183.
14. Hu RJ, Liu Q, Ma JY, Zhou J, Liu G. Preoperative lymphocyte-to-monocyte ratio predicts breast cancer outcome: A meta-analysis. Clin Chim Acta 2018;484:1-6. doi: 10.1016/j.cca.2018.05.031.
15. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: Methodological issues. Platelets 2002;13:301-6. doi: 10.1080/095371002220148332.
16. Ma Y, Zhang J, Chen X. Lymphocyte-to-monocyte ratio is associated with the poor prognosis of breast cancer patients receiving neoadjuvant chemotherapy. Cancer Manag Res 2021;13:1571-80. doi: 10.2147/CMAR.S292048.
17. Williams PT. The role of family physicians in the management of cancer patients. J Cancer Educ 1994;9:67–72. doi: 10.1080/08858199409528273.
18. Atlal Abusanad, humaid Al-Shamsi, Tele-Oncology: An Emerging Technology in Developing Countries during the COVID-19 Pandemic, Emirates Med J Medical, 2021; 2 (1): 13-15. http://doi.org/10.2174/0250688201999201109160857. Available from: https://www.eurekaselect.com/article/111292.
19. Seretis C, Seretis F, Lagoudianakis E, Gemenetzis G, Salemis NS. Is red cell distribution width a novel biomarker of breast cancer activity? Data from a pilot study. J Clin Med Res 2013;5:121-6. doi: 10.4021/jocmr1214w.
20. Azamjah N, Soltan-Zadeh Y, Zayeri F. Global trend of breast cancer mortality rate: A 25-year study. Asian Pac J Cancer Prev 2019;20:2015-20. doi: 10.31557/APJCP. 2019.20.7.2015.
21. Edechi CA, Ikeogu N, Uzonna JE, Myal Y. Regulation of immunity in breast cancer. Cancers (Basel) 2019;11:1080. doi: 10.3390/cancers11081080.
22. Savas P, Salgado R, Denkert C, Sotiriou C, Darcy PK, Smyth MJ, *et al.* Clinical relevance of host immunity in breast cancer: From TILs to the clinic. Nat Rev Clin Oncol 2016;13:228-41. doi: 10.1038/nrclinonc.2015.215.
23. Rana AP, Kaur M, Zonunsanga B, Puri A, Kuka AS. Preoperative peripheral blood count in breast carcinoma: Predictor of prognosis or a routine test. Int J Breast Cancer 2015;2015:964392. doi: 10.1155/2015/964392.
24. Dezayee ZMI, Al-Nimer MSM. The clinical importance of measurement of hematological indices in the breast cancer survivals: A comparison between premenopausal and postmenopausal women. World J Oncol 2016;7:1-4. doi: 10.14740/wjon956e.
25. Ni XJ, Zhang XL, Ou-Yang QW, Qian GW, Wang L, Chen S, *et al.* An elevated peripheral blood lymphocyte-to-monocyte ratio predicts favorable response and prognosis in locally advanced breast cancer following neoadjuvant chemotherapy. PLoS One 2014;9:e111886. doi: 10.1371/journal.pone.0111886.
26. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: Crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 2013;13:759-71. doi: 10.1038/nrc3611.
27. Ménétrier-Caux C, Ray-Coquard I, Blay JY, Caux C. Lymphopenia in cancer patients and its effects on response to immunotherapy: An opportunity for combination with

Cytokines? J Immunother Cancer 2019;7:85. doi: 10.1186/s40425-019-0549-5.

28. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74. doi: 10.1016/j.cell.2011.02.013.
29. Arkew M, Gemechu K, Haile K, Asmerom H. Red blood cell distribution width as novel biomarker in cardiovascular diseases: A literature review. J Blood Med 2022;13:413-24. doi: 10.2147/JBM.S367660.
30. Atwa ET, Omar HM, Amin A, Hammad M. Red cell distribution width and mean platelet volume in rheumatoid arthritis patients: Its association with disease activity. Reumatol Clin (Engl Ed) 2022;18:399-405. doi: 10.1016/j.reumae.2021.04.011.
31. Lu F, Pan S, Qi Y, Li X, Wang J. The Clinical Application Value of RDW, CA153, and MPV in Breast Cancer. Clin laboratory, 2021;67. https://doi.org/10.7754/Clin.Lab.2020.200507.
32. Simões R, Ferreira AC, Silva LM, Sabino AP, Carvalho MDG, Gomes KB. Evaluation of the RDW index (red cell distribution width) in women with breast cancer treated with doxorubicin in a one-year follow-up study. Diagnostics (Basel) 2023;13:1552. doi: 10.3390/diagnostics13091552.
33. Goldstein LJ, Perez RP, Yardley D, Han LK, Reuben JM, Gao H, *et al.* A window-of-opportunity trial of the CXCR1/2 inhibitor reparixin in operable HER-2-negative breast cancer. Breast Cancer Res 2020;22:4. doi: 10.1186/s13058-019-1243-8.