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Hemogram index parameters in the evaluation of male breast cancer and inflammatory response: a case-control study

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SUMMARY

OBJECTIVE: Our aim was to investigate the hemogram index parameters and their clinical significance in the evaluation of the inflammatory response of patients with male breast cancer, who are rarely observed in the literature.

METHODS: In total, 22 (n=22) healthy male and 28 (n=28) male breast cancer patients without synchronous/metachronous tumors were included in this study. They were grouped as the healthy male control group (Group 1) and the male breast cancer patient group (Group 2). The male breast cancer was divided into two subgroups, namely, early stage [(stage: 0/I/II) (Group 2A)] and late stage [(stage: III/IV) (Group 2B)], and their hemogram index parameters were compared.

RESULTS: A significant (p>0.05) increase was observed in neutrophil/lymphocyte ratio (NLR) and·platelet/lymphocyte ratio (PLR) values in the late stage (Group 2B: stage III/IV) compared to the early stage (Group 2A: stage 0/I/II) and healthy control (Group 1) groups.

CONCLUSIONS: In male breast cancer patients, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio values were significantly higher as the stage of cancer increased. These readily available simple tests can be used to evaluate the host's inflammatory response in male breast cancer.

KEYWORDS: Male breast cancer. Neutrophil. Platelet. Lymphocyte. Monocyte.

INTRODUCTION

Male breast cancer (MBC) is a rare disease accounting for approximately 0.5% of all cancer cases in the United States and 0.8% in Turkey[1,2]. Increasing evidence has recently shown that not only the tumor characteristics but also the inflammatory response of the host are effective in the development, progression, and prognosis of neoplastic diseases, including female breast cancers (FBCs)[3]. Although liquid biopsies (such as circulating tumor cells, circulating DNA, circulating miRNA, circulating lncRNA, and exosome) have been developed in the evaluation of treatment response and prognosis in patients with breast cancer, their use is limited due to their high cost[4,5].

In this study, we aimed to investigate the low-cost hemogram index parameters (HIPs) and their clinical importance in the evaluation of the inflammatory response of MBC patients, who are rarely seen in the literature.

METHODS

Ethical approval

Local ethics committee approval (dated: August 13, 2021, decision no.: 2902) was obtained.

Selection of patients

Within the scope of the study, the files of 34 MBC patients with code C50 who stayed in the hospital between March 1, 2006, and March 1, 2020, were reviewed retrospectively.

Notably, 28 (n=28) primary MBC patients without synchronous/metachronous tumors were included in this study. The control group consisted of 22 (n=22) healthy men over the age of 18 years who had normal breast examination and breast ultrasonography results, had normal HIP values, and were matched with MBC patient groups in terms of age and gender.

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A total of six patients with synchronous/metachronous tumors were excluded from this study. Five of the MBC patients who were excluded from this study were in the early stage, and one was metastatic. The patients' estrogen receptor (ER) and progesterone receptor (PR) were positive. Human epidermal growth factor receptor 2 (HER2) was positive in a patient with early-stage MBC. The histopathological examination revealed invasive ductal cancer (IDC) in five patients and invasive papillary cancer in one patient.

Hemogram index parameters and study design

The patients' HIP [absolute leukocyte count, i.e., white blood cells (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute platelet count (APC), absolute neutrophil count/absolute lymphocyte count ratio (NLR), absolute neutrophil count/absolute monocyte count ratio (NMR), absolute platelet count/absolute lymphocyte count ratio (PLR), absolute lymphocyte count/absolute monocyte count ratio (LMR), mean platelet volume (MPV), and red blood cell distribution width (RDW)] values, histopathological data, and disease staging were recorded at the time of diagnosis. The groups were divided into two groups, namely, the healthy control group (Group 1) and the MBC group (Group 2). MBC patients were divided into subgroups as Group 2A (stage 0/I/II) and Group 2B (stage III/IV), and their HIP values were compared by the XN 9000® (Sysmex, Kobe, Japan) device[5-7].

Statistical Methods

Mean, standard deviation, median, minimum–maximum value frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov–Smirnov test. The independent samples *t* test and Mann-Whitney U test were used for the comparison of quantitative data. The χ^2 test was used for the comparison of qualitative data. The SPSS software version 27.0 was used for statistical analyses.

RESULTS

The most common symptom at admission in the MBC patients included in this study was a mass with 89.3%. Of the patients, 85.8% underwent surgery. Of the patients undergoing surgery, 64.3% underwent mastectomy + axillary lymph node dissection (MRM or modified radical mastectomy), 17.9% underwent mastectomy + sentinel lymph node biopsy (MSLNB), 3.6% underwent palliative mastectomy (PM), and 14.2% underwent diagnostic tru-cut biopsy (Bx). In the histological examination, 64.3% were grade (G) 2, and lymphovascular invasion (LVI) was positive in 53.6%. The most common histological type was IDC. Of the patients, 92.9% had ER+, 78.6% PR+, 71.4% HER2– tumors, and 50% were in stages III and IV at the time of diagnosis (Table 1).

The mean age of Group 1 (control) and Group 2 (MBC) were 61.0±8.3 and 60.6±10.6 years, respectively. The mean age of Group 2A (stage: 0/I/II) and Group 2B (stage: III/IV) were 63.1±11.5 and 60.1±13.9 years, respectively. No significant difference ($p>0.05$) was found between the main groups and subgroups in terms of age and gender distribution of the patients. When comparing the HIPs, no significant difference ($p>0.05$) was observed in the values of WBC, ANC, ALC, AMC, APC, RDW, PDW, and MPV (Tables 2 and 3).

When comparing the healthy control group (Group 1) and the MBC group, no significant difference ($p>0.05$) was observed between the HIP values. NLR and PLR values increased significantly ($p>0.05$) in the late (Group 2B: stage III/IV) disease stage compared to the early stage (Group 2A: stage 0/I/II) and healthy control (Group 1) groups. Although the LMR value was significantly lower ($p<0.05$) in the late-stage (Group 2B: stage III/IV) patients compared to the healthy control group (Group 1), there was a noticeable decrease (Group 2A: 4.29±1.67 *versus* Group 2B: 2.75±1.53), which had no significant relationship ($p>0.05$) with disease staging. There was no significant difference ($p>0.05$) between the healthy control group (Group 1) and the early-stage (Group 2A: 0/I/II) patients group (Table 3).

DISCUSSION

The incidence of MBC represents less than 1% of breast cancers worldwide[1,2,8]. A mass in the breast, observed in 75–81% of patients, is the most common symptom. MBC patients are at later stages (stage III/IV) compared to FBC patients at the time of the diagnosis[9,10]. The incidence of stage III/IV cancer at admission is >60% in Africa, <40% in North America and Western European countries, and between 40% and 60% in Eastern Europe and South America. The reasons for admission at later stages are reported to be race, low socioeconomic status, lack of awareness about the disease, and uncertainties in the characterization of high-risk patients for screening in the literature[8,11-17]. In our study, the most common symptom was a breast mass, and 50% of them were at late stages at the time of diagnosis. Our results were better than the data available in the African literature and worse than those in developed countries.

Table 1. Distribution of clinicopathological data of male breast cancer patients

		n	%
Symptoms	Mass	25	89.3
	Mass and ulcerated	3	10.7
Surgery or diagnosis	MRM	18	64.3
	Mastectomy+SLNB	5	17.9
	Palliative mastectomy	1	3.6
	Biopsy	4	14.2
Histological type	DCIS	1	3.6
	IDC	21	74.0
	Mix type	5	17.8
	Special type	1	3.6
Tumor size category	pTis	1	3.6
	pT1	8	28.6
	pT2	9	32.1
	pT3	0	0.0
	pT4	10	35.7
Nodal category (N)	pN0	10	35.7
	pN1	10	35.7
	pN2	6	21.4
	pN3	2	7.2
Nodal status	Yes	18	64.3
	No	10	35.7
Metastasis (M)	M1	6	21.4
	M0	22	78.6
Stage	Stage 0	1	3.6
	Stage I	5	17.8
	Stage II	8	28.6
	Stage III	8	28.6
	Stage IV	6	21.4
Grade (G)	G1	0	0.0
	G2	18	64.3
	G3	6	21.4
	Missing	4	14.3
ER status	ER<1	1	3.6
	ER≥1	26	92.8
	Missing	1	3.6
PR status	PR<1	5	17.8
	PR≥1	22	78.6
	Missing	1	3.6
HER2 status	Yes	4	14.3
	No	20	71.4
	Missing	4	14.3
Lymphovascular invasion	Yes	15	53.6
	No	4	14.3
	Missing	9	32.1

MRM: modified radical mastectomy; SLNB: sentinel lymph node biopsy; DCIS: ductal carcinoma in situ; IDC: invasive ductal cancer; T: tumor size; N: nodal category; M: metastasis; ER: estrogen receptor; PR: progesterone receptor; HER 2: human epithelial growth factor receptor-2.

There is a need for regional studies to reveal the reasons for the late admission of patients.

In the African literature, 61.5–88.9% and 46.5% of patients in developed countries have axillary lymph node metastases at the time of diagnosis[11,12,14]. Although breast-conserving surgery and SLNB are alternative options in the treatment of early-stage (stage 0/I/II) MBC, MRM is still the standard surgical treatment method in recent days[11,14,18,19]. In locally advanced (stage III) MBC, staged surgical mastectomy can be performed after preoperative systemic chemotherapy (10). Patients with metastatic (stage IV) MBC are younger (≤65 years old), those with T1 tumors or those who have undergone surgical mastectomy have better survival rates than those who have not undergone a surgical intervention[20]. According to the immunohistochemical evaluation of the patients, 83–96% had ER+, 81–96% had PR+, and 10.6–35.1% were HER2 positive, and the most common histological type was IDC, which was observed in 80–90% of the patients[13,15,17]. More than half of these patients had LVI, and the predominant histological grade was G2[8-13,15,17]. In terms of histopathological evaluation and surgical treatment, our results are in accordance with the literature.

In breast cancers, males and females have similar prognostic factors. The main prognostic factors associated with disease-related survival are as follows: G, stage, hormone receptor status, tumor size, and lymph node status[21]. Recent studies on FBC have shown that patient-related inflammatory factors play a role in tumor initiation, formation, development, recurrence, metastasis, and treatment response. High NLR, PLR, and low LMR are reported as prognostic factors associated with survival[3,22,23]. In the study by Sun et al. comparing HIP values of healthy and FBC patients, MPV, RDW, NLR, and PLR values were found higher in FBC patients[6]. In a similar study, Rana et al. observed a decrease in the mean lymphocyte count as the stage of FBC patients increased[7]. In their study conducted on patients with metastatic FBC, Lee et al. reported that overall survival was shorter in patients with low ALC[24]. This is related to the decrease in the number of CD8+ T lymphocytes, which is the basic mechanism of tumor immunity, or the suppression of T-lymphocyte activity by neutrophils, which develop secondary to the increase in interleukin-8 secreted from the tumor. In addition, tumor angiogenesis and stroma formation are supported by the effect of vascular endothelial growth factor secreted from platelets[6,23]. It is reported that these easily accessible parameters may be useful in the management of FBC patients. However, due to the lack of studies on MBC and HIP in the literature, our knowledge is based on the data of WBC patients.

Table 2. Comparison of hemogram index parameters between control group and breast cancers.

	Group 1 (control)			Group 2 (stage 0/I/II/III/IV)			p-value
	Median	Mean±SD/n (%)		Median	Mean±SD/n (%)		
Male		22	100		28	100	1.000[x2]
Age	59.5	61.0±8.3		60.0	60.6±10.6		0.399[m]
WBC (×10⁹/L)	7.50	7.65±1.42		7.08	8.08±2.63		0.953[m]
Neutrophil (×10⁹/L)	4.28	4.45±0.79		4.29	4.89±2.58		0.845[m]
Lymphocyte (×10⁹/L)	2.38	2.37±0.89		2.15	2.07±0.57		0.115[t]
Monocyte (×10⁹/L)	0.57	0.59±0.19		0.60	0.89±1.02		0.551[m]
Platelet (×10⁹/L)	234.0	238.4±64.0		225.5	246.4±86.0		0.718[t]
RDW	13.3	14.0±1.8		13.9	14.1±1.2		0.197[m]
PDW	16.0	21.2±14.4		15.7	19.6±13.1		0.314[m]
MPV (fL)	8.90	9.31±1.81		9.40	9.34±1.33		0.660[t]
NLR	1.95	2.39±2.18		2.19	2.72±2.26		0.423[m]
PLR	101.2	103.7±45.1		108.9	127.5±53.8		0.123[m]
LMR	4.02	4.54±2.35		3.54	3.52±1.76		0.171[t]

SD: Standard deviation; WBC: white blood cells (×109/L); RDW: red blood cell distribution width (%); PDW: platelet distribution width (%); MPV: mean platelet volume (fL); NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio.[t]t test; [m]Mann–Whitney U test; [x2]χ^2 (Fisher's exact test).

Table 3. Comparison of hemogram index parameters between control group and subgroup breast cancers.

	Group 1 (control)			Group 2A (stage 0/I/II)			Group 2B (stage III/IV)			p
	Median	Mean±SD/n (%)		Median	Mean±SD/n (%)		Median	Mean±SD/n (%)		
Male		22	100		14	100		14	100	1.000[x2]
Age	59.5	61.0±8.3		67.0	63.1±11.5		63.5	60.1±13.9		0.757[A]
WBC (×10⁹/L)	7.50	7.65±1.42		6.80	7.43±2.10		8.18	8.73±3.01		0.354[K]
Neutrophil (×10⁹/L)	4.28	4.45±0.79		3.73	4.14±2.12		4.75	5.63±2.85		0.298[K]
Lymphocyte (×10⁹/L)	2.38	2.37±0.89		2.25	2.30±0.47		1.96	1.84±0.57		0.890[A]
Monocyte (×10⁹/L)	0.57	0.59±0.19		0.52	0.79±1.01		0.67	0.98±1.06		0.204[K]
Platelet (×10⁹/L)	234.0	238.4±64.0		220.5	240.7±103.3		228.5	252.1±67.9		0.870[A]
RDW (%)	13.3	14.0±1.8		13.8	13.8±0.9		14.0	14.4±1.4		0.157[K]
PDW (%)	16.0	21.2±14.4		14.5	15.8±8.8		16.2	23.4±15.7		0.196[K]
MPV (fL)	8.90	9.31±1.81		9.40	9.66±1.15		9.25	9.02±1.47		0.554[A]
NLR	1.95	2.39±2.18*		1.48	1.84±0.93*		2.78	3.59±2.84		0.034[K]
PLR	101.2	103.7±45.1*		97.5	105.6±38.9*		131.0	149.4±58.9		0.023[K]
LMR	4.02	4.54±2.35*		4.36	4.29±1.67		2.49	2.75±1.53		0.030[A]

SD: Standard deviation; WBC: white blood cells (×109/L); RDW: red blood cell distribution width (%); PDW: platelet distribution width (%); MPV: mean platelet volume (fL); NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio. Bold values denote statistical significance at p<0.05. [A]Analysis of variance; [K]Kruskal–Wallis (Mann–Whitney U test); [x2]χ^2 (Fisher's test); *Difference with Group 2B (stage III/IV).

In the literature, the only up-to-date publication on MBC patients and HIP belongs to Huszno et al., who reported that high PLR, NLR, and MLR values are associated with low overall survival in MBC patients[25]. In our study, as the MBC patients' disease stage increased, their NLR and PLR values also increased significantly (p<0.05) while a noticeable but nonsignificant (p>0.05) decrease was observed in LMR mean values (Group 2A: 4.29±1.67 *versus* Group 2B:

2.75±1.53). There was no significant (p>0.05) difference between the healthy control group and the MBC group. This was because it was affected by MBC patients at the early stage (Group 2A: 0/I/II). Our results are in accordance with the existing literature.

The main limitation to our study is that a survival study could not be conducted due to its retrospective design, the rarity of MBC patients, and its limited sample size. However, we believed that our results would provide some perspectives for prospective larger-scale studies.

CONCLUSION

As the disease stage increased in MBC, NLR and PLR values also increased significantly higher. These readily available simple tests can be used to evaluate the host's inflammatory response to MBC.

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AUTHORS' CONTRIBUTION

FD: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **HÖ:** Conceptualization, Formal Analysis, Investigation, Writing – review & editing. **KU:** Conceptualization, Formal Analysis, Investigation, Writing – review & editing. **SBH:** Methodology, Formal Analysis, Investigation, Writing – review & editing. **BO:** Formal Analysis, Methodology, Writing – review & editing. **ŞÇ:** Methodology, Formal Analysis, Investigation, Writing – review & editing. **EF:** Formal Analysis, Investigation, Writing – review & editing. **SS:** Methodology, Writing – original draft, Writing – review & editing.

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