Future Journal of Pharmaceutical Sciences

RESEARCH

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Down-regulation of *MSH3* and *MSH6* genes in female breast cancer patients receiving taxane-based therapy

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Abstract

Background The DNA in each cell in our body is constantly in danger of becoming damaged. Most DNA damage gets repaired straight away via many different proteins encoded by DNA—repair genes. MSH3 and MSH6 are pivotal DNA repair genes maintaining human genome integrity. Dysregulated expression of such genes has its implications resulting in developing of adverse reactions in cancer breast patients receiving taxanes. Cancer chemotherapy with some of taxane class of agents are associated with significant neurotoxicity, arthralgias and myalgias that may offset the therapeutic benefits of taxane use. Our aim is to identify gene expression pattern of MSH3 and MSH6 DNA mismatch repair genes in female breast cancer patients who develop adverse reactions to taxane-based therapy. One hundred and five patients with histologically proven breast cancer who received paclitaxel (PTX) as a single agent or combination therapy have been enrolled along with a group of 50 females with benign breast lesions serving as controls.Gene expression studies of mismatch repair genes (MMR) genes; *MSH3* and *MSH6*; have been performed by real-time PCR. Patients were divided into groups according to the determined type/grade of PTX-based toxicity and fold changes of both genes were estimated.

Results In the present work both MMR genes showed significantly lower expression in all the studied patients compared to benign cases as a control group. Toxicity findings were encountered in 75.2% of the studied patient cohort. The most common observed type of toxicity was peripheral neuropathy (PN), 58.1% of the studied patients. Both *MSH3* and *MSH6* genes were significantly down-regulated in the presence of high grade PN toxicity ≥ 2 ($p = 0.034$ and 0.01); diarrhea toxicity ($p = 0.02$ and 0.008); dyspnea ($p = 0.01$ and 0.016) respectively and bone pain ($p = 0.024$ for *MSH6* only).

Conclusion Dysregulated expression of MMR GENES [MSH3and MSH6] can be implicated in paclitaxel—induced toxicity experienced by some cancer breast patients.

Keywords Mismatch repair genes, Breast cancer, Taxane-based therapy, Toxicity prediction

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Background

Breast cancer among women is a global health problem with high morbidity and mortality. In 2020, it was the most commonly diagnosed women cancer with about 685,000 women died from the disease worldwide [1]. The overall costs of breast cancer management are related not only to the entire chemotherapeutic regimen, but also to potential chemotherapy induced side effects and costs of hospitalization. Taxanes are a class of drugs widely used to treat a variety of cancers, including breast, ovarian, lung, gastric, and head and neck [2]. The National Comprehensive Cancer Network Guidelines recommend taxanes for the treatment of early-stage and metastatic breast cancer [3]. It has been proved that taxanes have positive impact on the natural history of breast cancer [4].

Many breast cancer patients receiving a taxane-based chemotherapy have inter-individual variability in response and dosages which are often limited by toxic side effects [5]. These patients who are at high risk of toxicity need to be identified before receiving taxanes. Toxicity occurrence requires close monitoring of patients and necessitates decreasing or discontinuing taxane treatment. Thus, clinicians can tailor more informed decisions for patients being treated with those chemotherapeutic agents. A major factor that influences drug exposure and patient sensitivity is variation in the patient's genome [6].

There are six DNA repair pathways to stabilize and maintain integrity of the human genome during DNA recombination and replication [7].These functions are accomplished through the repair of bases, nucleotide excisions, double-strand break and DNA mismatch (MMR) [8]. Malfunction of MMR pathways are responsible for DNA instability, promoting tumor genesis, progression, and therapeutic resistance [9, 10]. Deregulated expression of DNA repair genes frequently found in tumors postulated that DNA repair pathways can be targeted in cancer treatment and indicated their role in personalized therapy [11].

Little is known about the MMR altered expression in blood of breast cancer patients predicting chemotherapeutic toxicity. By this work we aimed to identify gene expression pattern of *MSH3* and *MSH6* DNA repair genes in female breast cancer patients who develop adverse reactions to paclitaxel (PTX)-based therapy.

Patients and methods

Patients

Our study was conveyed in the period between 2020 and 2022; we did include one hundred and five female Egyptian patients with histologically proven breast cancer. They received PTX on a weekly basis in a dose of 80 mg/m^2 IV over 3 h as a single agent or combination therapy; on either adjuvant or palliative bases. A cohort of 50 females with benign tumor had been enrolled as a control group for gene expression fold change estimation. Patients' records were fetched for collection of demographic and clinical data for this study. The study was performed after at least four cycles of treatment to determine toxicity findings. Inclusion criteria included age ($\geq$18 years), performance status of less than 3 in accordance to the Eastern Cooperative Oncology Group criteria (ECOG) [12].

Patients with co-morbid disease conditions like severe liver disease or renal failure prior to treatment, peripheral neuropathy or vascular complications from hypothyroidism, hypercholesterolemia, hypertension, diabetes, varicella zoster, peripheral vascular disease, and autoimmune disease with vasculitis were excluded; these conditions are known to be associated with the development of peripheral neuropathy [13]. Grades of toxicities were identified based on patients' clinical and laboratory findings. All patients were subjected to full history taking and thorough clinical examination. They were categorized according to the presence/absence of toxicity. Grading was reported according to Common Toxicity Criteria (CTCAE) version 4.0 [14, 15].

Blood sampling

Fresh peripheral blood samples (10 mL) were collected in K2-EDTA, and plain blood collection tubes (Becton, Dickinson and Company) for complete blood count, gene expression studies and biochemical analyses.

Biochemical and hematological assays

Complete blood count and biochemical analyses including fasting glucose, liver function tests (ALT and AST), and renal function tests (blood urea and creatinine) were sequentially assessed for cancer breast patients within 48 h before chemotherapy, all displayed laboratory tests were performed in same setting.

RNA extraction

Whole blood RNA extraction was performed promptly after specimen collection using RNeasy Mini Kit (QIAGEN, Strasse 1 40724 Hilden, Germany), according to the manufacturer's guidelines. Integrity and quality of the purified RNA was measured in duplicates by Nano Drop 2000c spectrophotometer® (Thermo Fisher Scientific Inc., DE, USA).

Real-time PCR assay

Preparation of cDNA template using high-capacity cDNA synthesis kit (Applied Biosystems, USA) was accomplished according to manufacturer's guidelines and stored frozen at −20 °C till further analysis. Real-time

PCR was performed using Quant Studio™ 12 K Flex Real-Time PCR platform (Applied Biosystems-Life Technologies, CA, USA). Commercially available TaqMan Gene Expression assays were employed; *MSH3* (Hs00989003_m1, cat no. 4448892) *and MSH6* (Hs00943000_m1, cat no.4331182). Thermal profiles were used as recommended by the manufacturer. Data analysis and quantification was based on the $\Delta\Delta C_T$ method with normalization of the raw data to β2 microglobulin (*B2M*) housekeeping gene (Hs00187842_m1, cat no.4331182). All assays were supplied by Thermo Fisher Scientific, Applied Biosystems-Life Technologies, CA. USA.

Statistical analysis

All test data was converted and manipulated by using SPSS software program version 20.0. Data was analyzed, mean and standard deviation or standard error of mean and range were calculated as regarding quantitative data as age, tumor size, biochemical laboratory results and fold change of *MSH3* and *MSH6* genes while qualitative data as sex, smoking behavior, menopause, family history, pathological profile, ER, PR, HER2 and presence of toxicity and their grades were presented by number and percent. One sample t test was applied to determine fold change difference between patients and controls. Comparison of fold change of *MSH3* and *MSH6* among studied breast cancer patients as regards presence of toxicity was done using t test and p value was established to determine the statistically significant difference between two groups. Logistic regression analysis was used to find out any relationship between different variables and the presence of toxicities. The differences between groups and variables' associations were considered statistically significant when $p < 0.05$, and considered highly statistically significant when $p < 0.01$.

Results

Demographic data of the studied breast cancer patients and control group are summarized in Table 1. PTX was administered on a weekly basis in a dose of 80 mg/m^2 IV over 3 h as an adjuvant in 41%, neo-adjuvant in 48.5% or palliative in 4.7% of the studied patients. Six patients received hormonal therapy, some patients got PTX with other chemotherapies e.g. Epirubicin–Cyclophosphamide (EC), (n = 35, 33.3%), or doxorubicin hydrochloride (Adriamycin) and cyclophosphamide (AC), (n = 48, 45.7%). Pathological profile and tumor characteristics of patients are presented in Additional file 1: Table S1, Biochemical & hematological results of the studied breast cancer patients are presented in Additional file 1: Table S2.

The study was performed after at least four cycles of treatment to determine toxicity findings. Different types

Table 1 Demographic and clinical data of the breast cancer studied patients and control

Variable		Cases N = 105 n, (%)	Controls N = 50 n, (%)
Age (years)	Mean ± SD	53.05 ± 9.9	47.05 ± 8.9
	range	27.0–73.0	25.0–70.0
Sex	Female (ALL)	105 (100.0%)	50 (100.0%)
Smoking	Passive	5(4.8)	2 (4)
	No	100 (95.2)	48 (96)
Menopause	Post	53 (50.5)	23 (46)
	Pre	52 (49.5)	27 (54)
F.H of breast cancer	Negative	77 (73.3)	35 (70)
	Positive	28 (26.7)	15 (30)
ECOG-PS	1	93(88.6)	NA
	2	12 (11.4)	

N number; *F.H* family history, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *NA* non applicable

Table 2 Toxicity types and grades among the studied patients

Toxicity type		Cases N = 105 no. (%)
Number of toxicities	No symptom	26 (24.8)
(% out of total cases)	One symptom	14 (17.7)
	2	22 (27.8)
	3	26 (33.0)
	4	9 (11.4)
	5–9 symptoms	8 (10.0)
Diarrhea	Yes	21 (20.0)
Grade:	1	6 (28.6)
(% of positive cases)	2	8 (38.1)
	3	7 (33.3)
Gastritis	Yes	19 (18.1)
Grade:	1	11 (57.9)
(% of positive cases)	2	5 (26.3)
	3	3 (15.8)
Fatigue	Yes	22 (21.0)
Grade:	1	20 (90.9)
(% of positive cases)	3	2 (9.1)
Skin rash	Yes	3 (2.9)
Grade:	1	2 (66.7)
(% of positive cases)		
Nail damage	Yes (all grade 1)	2 (1.9)
Nausea	Yes	19 (18.1)
Grade:	1	10 (52.6)
	2	8 (42.1)
	3	1 (5.3)
Vomiting	Yes	17 (16.2)
Grade:	1	11 (64.7)
(% of positive cases)	2	5 (29.4)
	3	1 (5.9)
Stomatitis	Yes (grade1)	1 (1.0)
Peripheral neuropathy	Yes	61 (58.1)
Grade:	1	24 (39.3)
(% of positive cases)	2	33 (54.1)
	3	3 (4.9)
	4	1 (1.6)
Dyspnea	Yes	8 (7.5)
Grade:	1	7 (87.5)
(% of positive cases)	2	1 (12.5)
Bone pain	Yes	60 (57.1)
Grade:	1	43 (71.7)
(% of positive cases)	2	13 (21.7)
	3	4 (6.7)

of toxicities upon PTX-based therapy were detected in 75.2% of patients. Patients with grades 0–1 toxicity were defined as absent or mild toxicity group while patients with toxicity grade ≥ 2 was considered the group of high severity grade. Chemotherapy induced peripheral neuropathy (CIPN) was the most frequent type of toxicity found in our cohort of patients (n = 61, 58.1%) with CIPN grade ≥ 2 seen in 60.6% of them. Toxicity types and grades among the studied patients are demonstrated in Table 2.

In the present work, highly significant deregulated expression of both DNA repair genes (*MSH3* and *MSH6*) had been detected when compared to benign cases with $p < 0.001$ as shown in Fig. 1. Table 3 showed the fold change in *MSH3* and *MSH6* genes' expression with and without toxicities of different types. The significant differences in expression are demonstrated in Fig. 2.

In the current study, down-regulation of *MSH6* gene was significantly observed in patients with PTX induced toxicity whatever its type or grade ($p = 0.038$). In clinical stage T ≥ 2 and treatment cycles over 16 there was statistically significant negative association between *MSH6* fold change and the presence of toxicity using logistic regression analysis with $p = 0.014$ (holding all other predictors constant, odds ratio: 6.967 and 95% confidence interval: 0.000–0.419). Down-regulation of both *MSH3* and *MSH6* genes have been significantly associated with PTX- induced diarrhea toxicity ($p = 0.02$ and 0.008 respectively) and with PTX-induced dyspnea ($p = 0.01$ and 0.016 respectively).

In patients developing bone pain with PTX intake *MSH-6*gene showed significant down-regulation with $p = 0.024$ and significant negative association by logistic regression analysis with $p = 0.02$ (holding all other predictors constant, odds ratio: 5.961 and 95% confidence interval: 0.011–0.678). Regarding the different PTX-CIPN grades, both *MSH3* and *MSH6* genes were significantly down-regulated in grades ≥ 2 when compared to grades 0–1 with $p = 0.034$ and 0.01 respectively. No associations have been detected between gene expression levels and the presence of anemia or elevated transaminases.

Discussion

Targeting genomic instability and MMR are now promising approaches in solid tumors' management [7]. Little is known about their expression alterations and association with PTX-induced toxicities in breast cancer. In the current study our cohort of patients received weekly PTX as an adjuvant in 41% and neo-adjuvant in 48.5% of them. The incidence of all grades of PTX induced toxicity was recorded among them to be 75.2% overall. PTX-CIPN was the most frequent type of toxicity found in 58.1% of our cohort of patients. The second prevalent toxicity type encountered was bone pain (57.1%) which has been attributed to PTX-induced arthralgia and myalgia.

These findings were in accordance with previous investigators [16, 17]. They documented that patients who have beaten cancer sometimes have poor quality of life due to development of a number of adverse reactions that may extend for a long time after completing their treatment and no effective method for prevention is available [17, 18]. Thus, the identification of predictive biomarkers for these intolerable reactions will add much to the efficiency of such chemotherapeutic drugs in breast cancer treatment. Many studies on lung cancer patients identified the association between MMR gene defects and platinum-based chemotherapeutic toxicity [19–21].

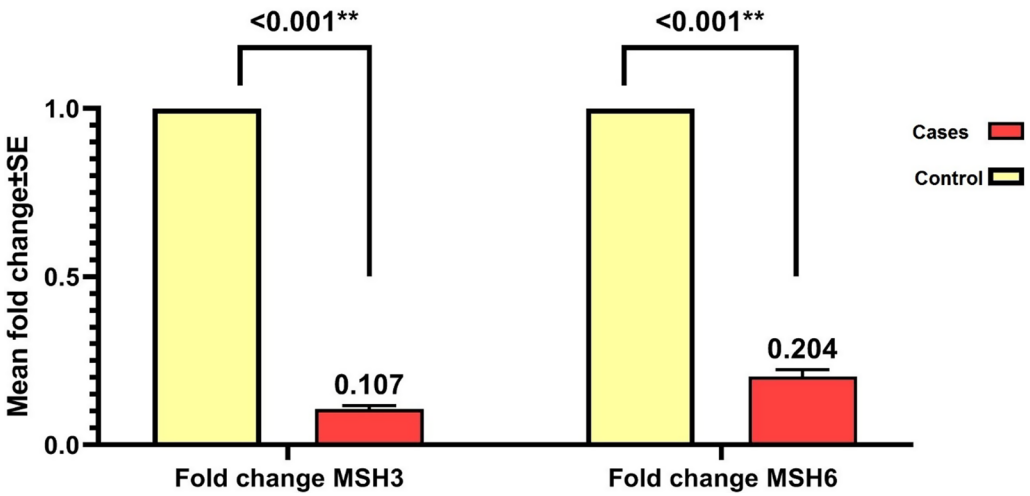

Fig. 1 Deregulated expression of both DNA repair genes (*MSH3* and *MSH6*) in malignant and benign cases

Table 3 Comparison of *MSH3* and *MSH6* genes' fold change among the studied breast cancer patients as regards presence of toxicity

Type of toxicity		*MSH3*fold change Mean ± SE	*MSH6*fold change Mean ± SE
Presence of toxicity	Yes	0.086 ± 0.01	0.179 ± 0.03
	No	0.139 ± 0.03	0.315 ± 0.07
p value		0.133	0.038*
Peripheral neuropathy	Yes	0.089 ± 0.02	0.182 ± 0.03
	No	0.114 ± 0.02	0.259 ± 0.05
p value		0.365	0.145
Peripheral neuropathy toxicity grade			
N = 68	0–1	0.127 ± 0.02	0.242 ± 0.03
N = 37	2–4	0.07 ± 0.02	0.136 ± 0.03
p value		0.034*	0.01*
Diarrhea	Yes	0.057 ± 0.01	0.122 ± 0.03
	No	0.108 ± 0.02	0.229 ± 0.03
p value		0.02*	0.008**
Dyspnea	Yes	0.043 ± 0.01	0.092 ± 0.04
	No	0.102 ± 0.01	0.218 ± 0.03
p value		0.01*	0.016*
Bone pain	Yes	0.075 ± 0.01	0.158 ± 0.03
	No	0.130 ± 0.03	0.281 ± 0.05
p value		0.062	0.024*
Fatigue	Yes	0.089 ± 0.04	0.167 ± 0.06
	No	0.10 ± 0.01	0.22 ± 0.03
p value		0.747	0.367
Gastritis	Yes	0.096 ± 0.05	0.178 ± 0.08
	No	0.098 ± 0.01	0.213 ± 0.03
p value		0.956	0.595
Nausea	Yes	0.091 ± 0.02	0.211 ± 0.06
	No	0.099 ± 0.02	0.206 ± 0.03
p value		0.819	0.943
Vomiting	Yes	0.098 ± 0.02	0.235 ± 0.06
	No	0.097 ± 0.02	0.202 ± 0.03
p value		0.980	0.625
Skin rash	Yes	0.097 ± 0.01	0.109 ± 0.08
	No	0.097 ± 0.07	0.211 ± 0.03
p value		0.999	0.448
Stomatitis	Yes	0.013	0.304
	No	0.095 ± 0.01	0.201 ± 0.02
p value		0.773	0.649

*Statistically significant ($p < 0.05$) **statistically highly significant ($p < 0.01$)

SE: standard error

In the present study, selected MMR genes (*MSH3* and *MSH6*) were studied to evaluate any altered expression in our patients with different types of toxicities upon PTX intake. *MSH3* and *MSH6*genes showed significantly lower expression in all breast cancer patients compared to benign cases as a control group. These findings are in agreement with other investigators [22, 23]. They assigned the MMR gene deficiency to their role in maintaining the genome stability by correcting base mismatch. Consequently, this function can eliminate any insult for carcinogenic changes through induction of apoptosis. Therefore, they considered *MSH3* and *MSH6* as tumor suppressor genes. Breast cancer harbor a wide range of defects in the MMR system, including gene mutations, down-regulation of RNA levels, promoter hyper-methylation and altered localization of the protein complexes at cellular level [24].

Previous investigators reported that MMR genes' deficiency increases the mutational rate of specific cancers and is often involved in its etiology [25, 26]. They showed that MMR gene single nucleotide polymorphisms were found in most individuals with MMR gene expression defects whether hereditary or acquired. Furthermore, decreased expression or deletion of MMR genes leads to defects in DNA repair hindering the normal DNA replication process and increases the risk of tumor development [24, 25].

In our study, down-regulation of *MSH6* gene was significantly associated with PTX induced toxicity whatever its type or grade indicating its toxicity predictive role. Our patients were stratified into groups according to the determined grade of PTX- CIPN. In the presence of high grade CIPN ≥ 2 significantly lower expression of both *MSH3* and *MSH6* genes was observed. Negative association was also significantly detected between both *MSH3* and *MSH6*genes' expression and PTX- induced diarrhea and dyspnea. In patients developing bone pain with PTX intake only *MSH6*gene showed significant down-regulation and significant negative association using logistic regression analysis. In this context, Liu et al. postulated that MMR gene defects can affect the effectiveness and adverse reactions of chemotherapy through the continuous accumulation of mutational events [21].

Mohiuddin et al. reported that PTX intake causes increased DNA fragmentation and activation of the DNA damage pathway. They also confirmed that PTX can inhibit cell proliferation and induce extrinsic and intrinsic apoptosis in human cancer cells in a concentration dependent manner [27]. This explains our finding of the significant negative association between *MSH6* fold change and the presence of toxicity in clinical stage T ≥ 2 and treatment cycles over 16 using logistic regression analysis. The study of Lodovichi et al.clarified that MMR genes are central players in DNA repair and that MutS proteins form two heterodimers, MutSα (MSH2-MSH6) and MutSβ (MSH2-MSH3) bind to the damaged DNA and recognize the mismatched base on the daughter strand. They postulated that their defects are closely

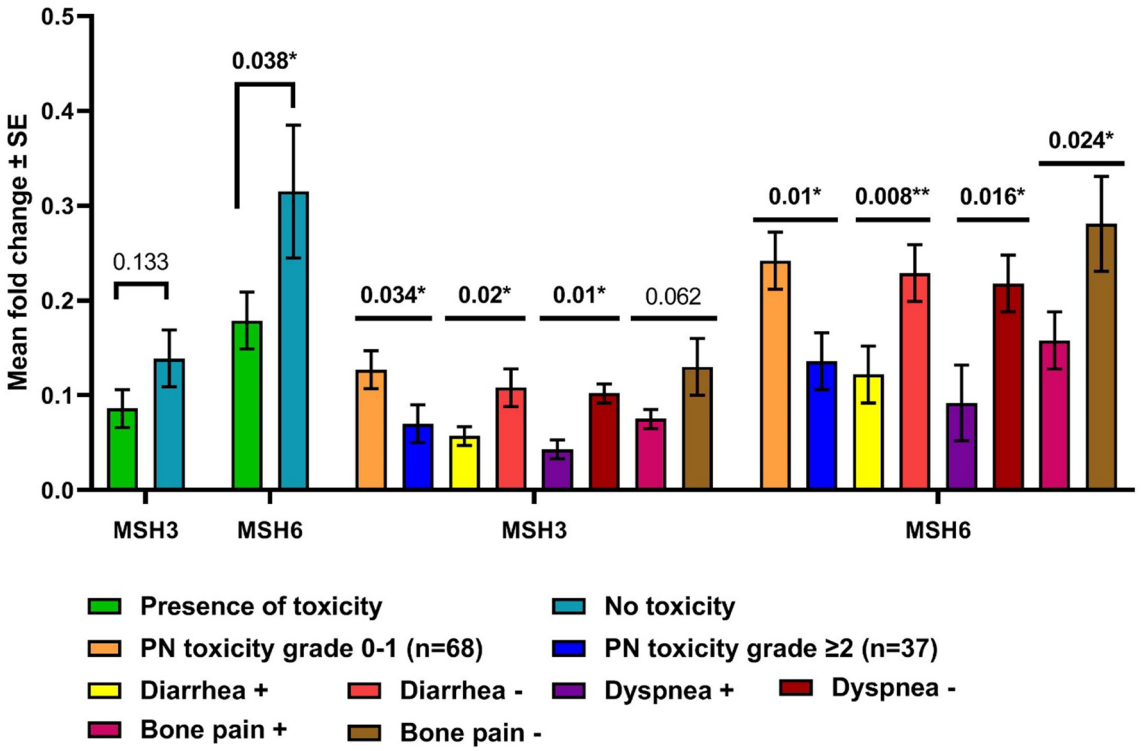

Fig. 2 Fold change in *MSH3* and *MSH6* genes' expression with and without toxicities of different types

related to chemotherapy resistance and that their re-expression can restore and improve the sensitivity to cancer treatment [28].

In conclusion, the present study showed the significant down regulation of MSH3 and MSH6 indicating the importance of monitoring such genes throughout the treatment cycles. Furthermore, our data clarified their predictive role in PTX-induced toxicities especially for *MSH6* gene. Therefore, MMR genes network can be considered candidate targets to increase the benefit/risk ratio of PTX therapy and to improve quality of life of breast cancer patients.

Abbreviations

PTX	Paclitaxel
MMR genes	Mismatch repair genes
PN	Peripheral neuropathy
ECOG	Eastern Cooperative Oncology Group criteria
CTCAE	Common Toxicity Criteria
EC	Epirubicin–Cyclophosphamide
AC	Adriamycin and cyclophosphamide
CIPN	Chemotherapy induced peripheral neuropathy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-023-00549-2.

Additional file 1. Table S1. Pathological profile and tumor characteristics of patients. **Table S2**. Biochemical & hematological results of the studied breast cancer patients.

Acknowledgements

The authors gratefully acknowledge the Science, Technology & Innovation Funding Authority through Capacity Building Program under grant (4880). The authors give special thanks to the Baheya Research Centre coordinator, Doaa Elsayed Mostafa Abo-kresha, for her efforts to provide us with all important data of the patients and make the path clear for us to implement our project

Author contributions

HRMA contributed to the project preparation, study design, submission for funding and writing draft of the manuscript. HRMA, MHI were responsible for the management of purchasing tasks and schedules. MHI coordinated specimen collection and transport and implemented a quality policy throughout the laboratory analysis workflow. MHI, DFA, SHAE, MMAW, SNAEF and MAAM contributed to laboratory analysis. Appropriate patient selection and data collection were performed and supervised by AH and MMK. Statistical analysis of data and tabulation of final results were accomplished by TMR. All authors have read and approved the final manuscript.

Funding
This research was financially supported by the National Research Centre (NRC), Egypt through project Grant no. E120507.

Availability of data and materials
All data and materials are available and can be submitted when needed, Corresponding Author is responsible person who should be contacted if someone wants to request the data from this study.

Declarations

Ethical approval and consent to participate
The study has been approved by both the Ethical Committee of the National Research Centre (no, 17–109) and Baheya-Research Ethics Committee (no. 0317) in accordance with the ethical standards of the Declaration of Helsinki.

Consent for publication
The authors declare no conflict of interest.

Informed consent
Informed written consent was obtained from all participants after the study objectives were explained and before blood sampling. Confidentiality of patient data was guaranteed.

Competing interest
The authors have declared that no competing interest exists.

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Received: 8 September 2023 Accepted: 23 October 2023
Published online: 31 October 2023

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