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The Oncogenic Influence of PIM1, Leptin and IL20 in Newly Diagnosed Breast Cancer Patients*

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Онкогенное влияние PIM1, лептина и IL20 у пациенток с впервые выявленным раком молочной железы**

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Aim. The underlying biological processes are crucial for understanding the process of breast tumorigenesis. Accordingly, the present study aims to investigate the impact of the expression of key cellular components [PIM1, leptin hormone (LEP) and Interleukin 20 (IL20)] in both of breast benign lumps and malignant cancer.

Materials and Methods. For this purpose, a serum blood samples were collected from all participants, including 50 newly newly diagnosed breast cancer, 23 with benign breast lumps and 45 age-matched healthy controls. The expression of PIM1 was assessed by qRT-PCR, while serum LEP and IL 20 were estimated via ELISA technique.

Results. The result of this study showed PIM1 gene expression was significantly ($p < 0.0134$) elevated in breast cancer patients at both malignant and benign level (2.76 ± 0.27 and 2.84 ± 0.42) relative to that of healthy controls. PIM1 expression seemed to be significantly influenced ($p > 0.05$) by breast cancer's age and menopausal status. Serum leptin levels also was significantly increased ($p < 0.001$) in patients diagnosed with breast cancer in comparison to that in benign breast lumps and healthy control (2 ± 0.14 vs. 0.69 ± 0.014 and 0.64 ± 0.03 ng/ml, respectively). Age and menopausal status were seeming to significantly ($p < 0.05$) affecting leptin serum levels of the assessed breast cancer patients. IL-20 serum levels showed a significant increase ($p < 0.05$) in patients with benign breast lumps compared to malignant breast cancer patients and healthy control groups.

Conclusion. Overall, the present study findings suggest that oncogenic PIM1 gene, LEP, and IL-20 expression are being selected to confer growth advantage for breast cells toward malignant transformation for both benign and malignant transformation of breast cell.

Keywords: breast cancer; oncogenic; PIM1; LEP hormone; IL20

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Цель. Понимание ключевых биологических процессов, лежащих в основе канцерогенеза, имеет решающее значение для изучения развития опухолей молочной железы. Целью настоящего исследования была оценка роли ключевых клеточных регуляторов [PIM1, гормона лептина (LEP) и интерлейкина-20 (IL-20)] в патогенезе как доброкачественных, так и злокачественных новообразований молочной железы.

Материалы и методы. В исследование были включены 50 пациенток с впервые диагностированным раком молочной железы, 23 пациентки с доброкачественными образованиями и 45 здоровых женщин контрольной группы, сопоставимых по возрасту. У всех участниц были взяты образцы сыворотки крови. Экспрессию PIM1 оценивали методом количественной ПЦР (qPCR), а сывороточные уровни лептина и IL-20 определяли с помощью иммуноферментного анализа (ИФА).

Результаты. Экспрессия гена PIM1 была достоверно повышена ($p = 0{,}0134$) как в группе пациенток с раком молочной железы, так и в группе с доброкачественными образованиями ($2{,}76 \pm 0{,}27$ и $2{,}84 \pm 0{,}42$ усл. ед. соответственно) по сравнению с контрольной группой. На уровень экспрессии PIM1 вероятно значимое влияние оказывали возраст ($p < 0{,}05$) и менопаузальный статус ($p < 0{,}05$) пациенток. Уровень лептина в сыворотке также был значимо повышен ($p < 0{,}001$) у пациенток с раком молочной железы ($2{,}00 \pm 0{,}14$ нг/мл) по сравнению с группами доброкачественных образований ($0{,}69 \pm 0{,}014$ нг/мл) и контроля ($0{,}64 \pm 0{,}03$ нг/мл). На сывороточный уровень лептина существенно влияли возраст и менопаузальный статус ($p < 0{,}05$). Концентрация IL-20 в сыворотке была достоверно выше ($p < 0{,}05$) в группе доброкачественных образований по сравнению с пациентками с раком молочной железы и контрольной группой.

Выводы. Полученные данные позволяют предположить, что повышенная экспрессия онкогенных факторов PIM1, лептина и IL-20 может способствовать пролиферации клеток и создавать благоприятные условия как для злокачественной трансформации, так и для формирования доброкачественных опухолей молочной железы.

Ключевые слова: рак молочной железы; онкогенез; PIM1; лептин; IL20

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Globally, the lifetime risk of breast cancer among women in the general population has increased, with the annual number of new cases and deaths expected to double by 2040 — reaching over 3 million new cases and 1 million deaths per year [1]. Greater efforts are needed to understand the biological events associated with its development. Indeed, oncogenic alterations can trigger cellular transformation and carcinogenesis [2]. Over the past three decades, breast cancer incidence and mortality rates have risen due to changes in risk factor profiles, improvements in cancer registry, and increased cancer detection [3]. Among the many cancer-associated genetic alterations, those that promote cellular expansion and proliferation are considered especially important in distinguishing driver mutations from passenger mutations. Due to variations in structural, histopathological, and biological features, breast cancer is one of the most heterogeneous diseases to study. It is also the leading cause of cancer-related death among Iraqi women, accounting for approximately one-third of all carcinoma cases reported in the country in 2019 [4].

Notably, oncogenes can induce genomic instability by increasing conflicts between replication and transcription. This suggests a crucial role for the oncogenic alterations in promoting tumorigenesis.

PIM1 is a proto-oncogene that phosphorylates, and regulates the activity of a number of key proteins encompassed in cellular proliferation, differentiation and apoptosis. Through its role in the inhibition of apoptosis and the regulation of cell division, *PIM1* has been linked to carcinogenesis [5]. In normal tissues, PIM1 expression is practically untraceable, however, in hematological malignancies and a large number of solid tumors, increased PIM1 expression has been correlated with the disease's stage [6]. This suggests that PIM1 expression could serve as a potential biomarker for cancer detection and progression.

Additionally, leptin hormone is a protein known for its influence in regulating body weight on a long-term basis, and has been shown to act as a mitogen, an inflammatory and pro-angiogenic factor that prompts cancer cell proliferation and tumor angiogenesis. As a mitogen, which refers to a small bioactive protein or peptide that induces division, several lines of evidence have suggested an involvement of leptin in cancer development [7]. Moreover, leptin signaling induces cancer stem cells, which are blamed for cancer recurrence and drug resistance [8]. Notably, the biological effect of leptin on inducing ovarian cancer cell growth was mediated by an increase in cyclin D1 and Mcl-1 expression after the activation of the PI3K/Akt and MEK/ERK1/2 signaling axes [9]. Leptin has the ability to stimulate epithelial–mesenchymal transition (EMT) which enables cells to gain a metastatic phenotype. Also, leptin has the potential to induce multiple immunosuppressive mechanisms, drug resistance, and evasion of apoptosis [10].

Furthermore, data suggests that leptin maintains cancer stem-like properties in gastric cancer cells. In the same manner, IL20, which is a protein normally involved in regulating angiogenesis, wound healing, epithelial cell proliferation, prevention of apoptosis of epithelial cells, regulation of differentiation of keratinocytes during inflammation, and the expansion of multipotential hematopoietic progenitor cells, has also been linked to tumorigenesis. A number of studies have reported tumor-promoting effects for IL20 in solid cancers [11].

Aberrant expression of genes or their products (proteins) often occurs at very large numbers of loci in malignant cells. Thus, it may be reasonable to use a panel of multiple markers to increase the patient 's stratification accuracy [12]. The present study sought to examine the expression patterns the expression patterns of PIM1, IL20, and LEP levels in relation to breast cancer at both benign and malignant levels in a set of Iraqi women patients. In addition to the assessment of their association with some breast cancer-related clinical features such as age, body mass index (BMI), and menopausal status.

Subjects and Methods

Fig. 1 summarizes the main methods and the outcome of the study. Starting with collecting samples and ending with analyzing the data.

Collection of blood sample

Blood samples were collected from a total number of 118 female participants with breast tumors and healthy controls (age range 30 to 70 years) during the period extending from December 2023 to June 2024 for molecular analysis. Samples and clinical data were obtained from the histopathology reports of Al-Yarmouk Teaching Hospital, Al- Amal Hospital, and Al-Alwiyya Maternity Teaching Hospital in Baghdad- Iraq. All patients were diagnosed according to the adopted hospital's clinical protocols through ultrasound and mammography examinations, the blood sera were collected from newly diagnosed women with malignant and benign breast tumor, depending on the histopathologist's examination, such as taking FNA and biopsies, to determine the degree of morphological changes and behavior of these cells. Participants were subdivided into three groups: Group 1 was assigned as control group consisting of 45 healthy females, Group 2 includes 23 patients with benign breast lumps, and Group 3 included 50 females with newly diagnosed

malignant breast cancer. Several demographic characteristics (age, weight, and height) were also collected from all participants in this study.

The study design has been approved by the College of Science Research Ethics Committee at the University of Baghdad (Ref. No. 0923/0074, dated the 25th of September 2023).

Estimation of human leptin (LEP) hormone and IL20 by ELISA technique

The serum level of leptin (LEP) hormone and IL20 was assessed in all investigated participants. For this purpose, serum was separated from the collected blood samples by centrifugation and stored in collection Eppendorf tubes. The human LEP ELISA kit (Cat. No. RE2739H/reed biotech) and IL 20 ELISA kit (Cat. No. ELK1291/ELK Biotechnology) were used according to the manufacturer's instructions.

Estimation of *PIM1* expression level by q-PCR analysis

For RNA extraction, a volume of 250 µl of the collected blood samples from each participant was added to 500 µl of TRIzol® LS reagent (Invitrogen company, USA) as (1:2) in Eppendorf tubes. The RNA was extracted using Easy Pure® Blood RNA Kit (TransGen Biotech Company, China) according to the protocol provided by the manufacturer. The extracted RNA was then converted to cDNA by ProtoScript® First Strand cDNA Synthesis Kit. GAPDH was used in this study as a housekeeping gene. All the primers sequence used in this study were from macrogen® (Korea). The primers design used in this study was used for the assessment of PIM1 relative expression are as following: *PIM1* forward 5′- GTCCTGCTGAAGAAGGTGAGC-3′, and *PIM1* reverse 5′-GAAGAGATCTTGCACCGGCTC-3′. GAPDH primers sets were adapted as a candidate HKG with the forward primer sequence of 5′-GTCTCCTCTGACTTCAA-3′, and GAPDH reverse primer of 5′-ACCACCCTGTTGCTGTA-3′. The quantitative real time qRT-PCR analysis method was used to evaluate *PIM 1* gene expression in the investigated subjects. The *PIM1* expression fold change was estimated through the adaptation of Livak's 2-ΔΔCt" formula [13].

Statistical analysis

All raw data were subjected to statistical analysis via SPSS (version 27, IBM), GraphPad Prism (version 8.4), and Microsoft Excel 2016. Statistical analyzes included analysis of variance One-Way ANOVA and independent t-tests. Data are presented as Mean ± S.E., with a p-value of < 0.05 considered statistically significant [14].

Results

***PIM1*gene expression in the newly diagnose breast cancer patients**

The results displayed a significant elevation ($p < 0.0134$) in expression of the PIM1 gene in breast cancer patients at both malignant and benign levels (2.76 ± 0.27 and 2.84 ± 0.42) compared to healthy women (table 1). This finding suggests that PIM1 expression is implicated in both benign and malignant transformation of breast cells (potentially being selected to confer a growth advantage for breast cells toward malignant transformation). Further detailed analysis of the PIM1 gene expression levels based on the different age categories of the assessed breast cancer patients showed that those diagnosed at older ages (61–70 yrs) seemed to have significantly ($p = 0.034$) higher expression

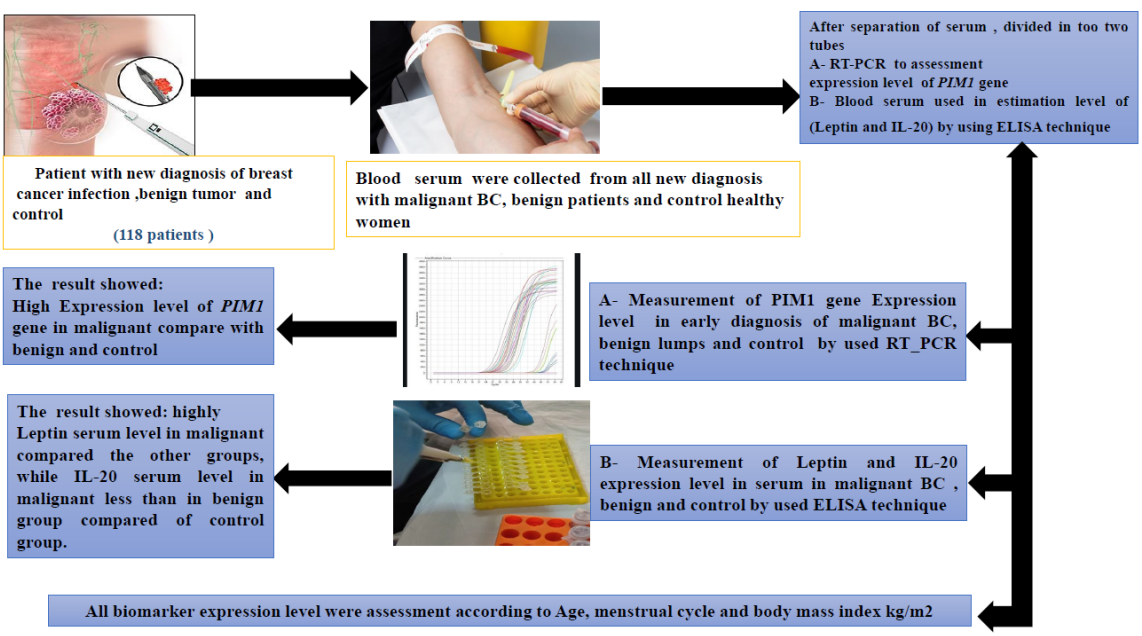

Fig. 1. Schematic overview of the main practical steps and principal finding

levels of PIM1 than patients presenting the disease at younger ages (30–40 yrs and 41–60 yrs). PIM1 expression average fold change was shown to be almost doubled in breast cancer cases diagnosed at older ages > 61 years: 4.25 ± 0.93. The younger women (aged) 30–40 yrs showed the second most dangerous aged group affected by cancer development: 2.7 ± 0.8, while 2.5 ± 0.27 was diagnosed in 41–60-year-olds. Similarly, PIM1 expression fold change was shown to increase significantly in post-menopausal newly diagnosed breast cancer patients than those presenting the disease in the pre-menopausal period (3.1 ± 0.42 vs. 2.2 ± 0.27, respectively). However, PIM1 expression does not seem to be affected by the body mass index (BMI) of the newly diagnosed breast cancer patients. PIM1 expression fold for diagnostic breast cancer patients with normal weight was 2.9 ± 0.63, while it was 2.8 ± 0.5 and 2.7 ± 0.32 for those within overweight and obese BMI categories (table 2) Fig. 2 (online suppl.).

Leptin serum levels assessment at breast cancer presentation

LEP serum levels were shown to increase significantly ($p < 0.001$) in patients diagnosed with breast cancer in comparison to those in benign breast lumps and healthy cases: 2 ± 0.14 vs. 0.69 ± 0.014 and 0.64 ± 0.03 pg/ml, respectively (table 3). Additionally, serum levels of LEP hormone were shown to be significantly higher ($p = 0.0148$) in breast cancer diagnosed at older ages > 60 years compared to those presenting the disease at younger ages: 2.8 ± 0.41 vs. 2.05 ± 0.5 for benign and 1.9 ± 0.155 for healthy women, respectively.

Table 1. *PIM1* expression fold level in different study groups of women with early-diagnosed breast cancer

		Parameters (Mean ± SE)
Groups	No.	PIM1 expression level
Control	45	1 ± 0
Benign	23	2.84 ± 0.42
Malignant	50	2.76 ± 0.27
P-value	-	0.0134*

Table 2. Association of *PIM1* expression with clinical parameters in women with early-diagnosed breast cancer

	Parameters (Mean ± SE)	
Age categories	**No.**	***PIM1*** expression level
30–40	16	2.7 ± 0.8
41–60	25	2.5 ± 0.27
61–70	32	4.25 ± 0.93
Eta-squared	-	0.083
P-value		0.034*
Menstrual status		
Premenopausal	32	2.2 ± 0.27
Postmenopausal	41	3.1 ± 0.42
Cohen's d	-	-0.502
P-value		0.047*
BMI (kg/m^2)		
Normal	9	2.9 ± 0.63
Overweight	27	2.8 ± 0.5
Obese	37	2.7 ± 0.32
Eta-squared	-	0.000
P-value		0.992 NS

Data are presented as mean ± standard error. *P < 0.05 indicates statistical significance; NS = not significant (p > 0.05)
•Eta-squared = one-way ANOVA effect size (small = 0.01, medium = 0.06, large = 0.14)
• Cohen's d = independent t-test effect size (small = 0.2, medium = 0.5, large = 0.8)

Table 3. LEP expression level in different study groups of women with early-diagnosed breast cancer

		Parameters (Mean ± SE)
Groups	No.	LEP expression level (ng/mL)
Control	45	0.64 ± 0.03
Benign	23	0.69 ± 0.014
Malignant	50	2 ± 0.14
P-value	-	0.001***

Table 4. Association of LEP expression in breast cancer study group based on age categories, menstrual cycle and BMI Kg/m^2

		Parameters (Mean ± SE)
Age categories	No.	LEP expression level (ng/mL)
30–40	10	2.05 ± 0.5
41–60	52	1.9 ± 0.155
61–70	11	2.8 ± 0.41
Eta-squared	-	0.098
P-value		0.0148*
Menstrual Cycle		
Premenopausal	35	1.47 ± 0.71
Postmenopausal	38	2.4 ± 0.95
Cohen's d	-	-0.792
P-value		0.0014**
BMI (kg/m^2)		
Normal	8	2.37 ± 0.11
Overweight	25	2.03 ± 0.29
Obese	40	1.9 ± 0.19
Eta-squared	-	0.013
P-value		0.737 NS

Data are presented as mean ± standard error. *p < 0.05, **p < 0.01 indicate statistical significance; NS = not significant (p > 0.05)
•Eta-squared = one-way ANOVA effect size (small = 0.01, medium = 0.06, large = 0.14)
• Cohen's d = independent t-test effect size (small = 0.2, medium = 0.5, large = 0.8)

Furthermore, women presenting with breast cancer postmenopausally were shown to have significantly ($p = 0.0014$) higher leptin levels than those diagnosed in the premenopausal status: 2.4 ± 0.95 and 1.47 ± 0.71, respectively (table 4). While leptin serum levels did not differ significantly ($p = 0.737$) between women presenting breast cancer at different BMI categories (normal weight vs. overweight vs. obese; 2.37 ± 0.11, 2.03 ± 0.29, 1.9 ± 0.19, respectively). The expression of LEP hormone was also presented in (Fig. 3, online suppl.).

IL20 serum levels assessment at breast cancer presentation

IL-20 serum levels showed significant differences ($p = 0.031$) between benign and malignant breast cancer patients in comparison to their healthy counterparts (table 5). This finding suggests potential involvement of IL20 as a stemness modifier that contributes to breast carcinogenic events. Conversely, the serum levels of IL20 did not show significant differences among the other different assessed age groups (table 6). IL-20 serum levels were comparable in both premenopausal and postmenopausal diagnosed breast cancer patients. Similarly, IL20 serum levels were almost the same in the assessed BMI subgroups of the investigated newly diagnosed breast cancer cases (fig. 4, online suppl.).

Table 5. IL20 expression level in different study groups of women with early-diagnosed breast cancer

		Parameters (Mean ± SE)
Groups	No.	IL20 expression level (ng/mL)
Control	45	0.64 ± 0.03
Benign	23	0.69 ± 0.014
Malignant	50	0.64 ± 0.009
P-value	-	0.031*

Table 6. Association of IL20 expression level in breast cancer study group according to age categories, menstrual cycle and BMI Kg/m²

	Parameters (Mean ± SE)	
Age categories	No.	IL-20 expression level (ng/ml)
30–40	8	0.66 ± 0.03
41–60	56	0.65 ± 0.012
61–70	9	0.62 ± 0.014
Eta-squared	-	0.022
P-value		0.586 NS
Menstrual Cycle		
Premenopausal	32	0.65 ± 0.02
Postmenopausal	41	0.64 ± 0.01
Cohen's d	-	-0.012
P-value		0.809 NS
BMI (kg/m2)		
Normal	7	0.65 ± 0.03
Overweight	23	0.63 ± 0.02
Obese	43	0.64 ± 0.012
Eta-squared	-	0.01
P-value		0.788 NS

Data are presented as mean ± standard error. *p < 0.05, **p < 0.01 indicate statistical significance; NS = not significant (p > 0.05)
•Eta-squared = one-way ANOVA effect size (small = 0.01, medium = 0.06, large = 0.14)
• Cohen's d = independent t-test effect size (small = 0.2, medium = 0.5, large = 0.8)

Discussion

Understanding why the breast is the most common organ in the female body affected by cancer is of great research interest. Consequently, efforts have been allocated to identify how transformation-associated biological alterations contribute to breast cancer initiation and progression [15, 16, 17]. The present study has identified a significant impact of the alteration in *PIM1* expression in the breast cancer pathogenesis. This is evident in patients with both benign breast lumps and breast cancer who have elevated levels of *PIM1* expression. As an oncogenic driver that requires the maintenance of a tumorigenic phenotype in MYC-expressing solid tumors [18], *PIM1* expression seemed to be needed to be maintained at a higher level for both breast pre-tumorigenic and malignant phenotypes. Notably, the *PIM1* overexpression was shown to be associated with older age and post-menopausal status in the assessed women with breast cancer cases. The debate about *PIM1* overexpression has gained fresh prominence with many arguing its role in tumorigenesis and treatment resistance in many different types of cancer [5]. This information could be used to develop *PIM1* directly-targeted interventions aimed at inhibiting its expression to investigate their potential in improving patient outcomes and spare them from treatment overdose.

A similar association has been observed for leptin serum levels in the assessed breast cancer cases where its levels were shown to increase in malignant breast tumor cases, especially those diagnosed at older ages (61–70 yrs) with an elevated level in the post-menopausal status. In this regard, a large body of evidence has suggested an involvement of high circulating leptin levels in a wide spectrum of solid tumors. As a proangiogenic, pro-invasive and mitotic factor, leptin has been blamed as a key contributor to breast cancer development [19]. This is quite an interesting research venue as the qualitative analysis of the circulating leptin level might help to gain insights into breast tumor types and their progression. The association between leptin and obesity is well-acknowledged due to its role in regulating appetite and energy expenditure [20]. However, obesity is known as

the most common tumor risk factor to create a mitogenic microenvironment that influences tumor initiation and progression. On the other hand, insulin is the most obesity-related hormone. The actions of insulin on adipose tissue, skeletal muscle, smooth muscle; and the liver can be related to the increased release of leptin in obese women [21]. This appears to be consistent with the finding of the present study that highlights elevated leptin serum levels in the assessed breast cancer cases. Apart from being a bridge from obesity to breast malignancy, leptin circulating levels and leptin receptors are overexpressed in multiple types of cancer and might be a useful biomarker for stratifying cancer patients into different prognostic categories.

While cytokines have been determined to be the most released molecules in the loss of immune tolerance in many diseases [22], serum levels of IL-20, which is linked to tumorigenesis via its involvement in the regulation of regulating angiogenesis, epithelial cells proliferation, and prevention of epithelial cells apoptosis [23], are in line with our finding, which showed a significant difference between the assessed breast cancer cases, especially those with benign breast lumps and their healthy counterparts, which indicates a role in lump initiation. Regardless, IL20 could play a critical role in enhancing the stem cell modifier and promoting the formation of an immunosuppressive microenvironment in BC patients [24]. Considering that women with benign breast lumps have a 70 % higher risk of developing breast cancer than those who are not, aberrant circulating levels of IL-20 could be useful components in the risk assessment of breast cancer [25]. It is noteworthy that, depending on the situation, cytokines such as IL-20 can have both pro- and anti-tumorigenic properties in some cases. A promising path toward the development of therapeutics is the comprehension of the dual function of cytokine IL20 within the TME and its interactions with the characteristics of breast cancer cells [26]. It has been indicated that these cytokines and their receptors are secreted in both pathological and physiological conditions. Thus, another related study recommends that the slight release of IL-20 during the early stages of tumor growth due to inflammation encourages the mutagenesis of tumor cells and accelerates their transformation into a highly malignant state in the future [27], as shown in the current study.

Thus, because benign illnesses frequently entail strong immunological and inflammatory responses and ILs, like IL-20, are generated primarily as part of a local inflammatory response and spill into circulation, interleukins may be somewhat higher in benign breast disease. While the TME may maintain localized cytokine activation in malignancy, however, to increase their chances of survival, many malignant tumors usually avoid or inhibit a variety of immune response mechanisms and immune cells.

As breast cancer is classified as the first among cancers affecting women in the Iraqi population, and it is associated with genetic and epigenetic alterations [28], consistent with the findings of the present study, several lines of evidence suggest a significant impact of IL-20 and its cellular receptor in the enhancement the stemness phenotype and promotion of the formation of an immunosuppressive microenvironment in breast tumor.

Conclusion

Collectively, the present study findings have highlighted the potential association of key cellular components (PIM1, leptin, and IL-20) with breast cancer diagnosis, prognosis, and presentation. This could be investigated further in a larger cohort of breast cancer cases to gain deeper insights into the cellular events that trigger such a devastating health issue.

Conflict of interest
The authors declare no conflict of interest in this work.

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Compliance with patient rights and principles of bioethics
All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the Declaration of Helsinki Protocol (2013). The study protocol was approved by the College of Science Research Ethics Committee at the University of Baghdad (Ref. No. 0923/0074, dated 25 September 2023). Written informed consent was obtained from all individual participants included in the study.

Authors' contributions
All authors made a substantial contribution to the conception of the work, preparation of study design as well as acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published, and agree to be accountable for all aspects of the work.

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