AUIQ Technical Engineering Science

Volume 2 | Issue 3 Article 9

2025

Evaluating IGF1 and IGF1-R Levels as Risk-Related Indicators and Early Detection Tools in Estrogen Receptor–Positive Breast Cancer

Randa M. Lua'i
Department of Chemistry, College of Sciences, Al- Nahrain University, Baghdad, Iraq,
randamohammad234@gmail.com

Khawla A. Kasar
Applied pathological Analysis department, College of Sciences, Al- Nahrain University, Baghdad, Iraq,
khawla.kasar@nahrainuniv.edu.iq

Marwa A. Hassan
Department of Medical Physics, College of Sciences, Al- Nahrain University, Baghdad, Iraq,
marwa@nahrainuniv.edu.iq

Recommended Citation

Lua'i, Randa M.; Kasar, Khawla A.; and Hassan, Marwa A. (2025) "Evaluating IGF1 and IGF1-R Levels as Risk-Related Indicators and Early Detection Tools in Estrogen Receptor–Positive Breast Cancer," *AUIQ Technical Engineering Science*: Vol. 2: Iss. 3, Article 9.
DOI: https://doi.org/10.70645/3078-3437.1050

AUIQ TECHNICAL ENGINEERING SCIENCE 2025;2:129–138

ORIGINAL STUDY

Evaluating IGF1 and IGF1-R Levels as Risk-Related Indicators and Early Detection Tools in Estrogen Receptor–Positive Breast Cancer

Randa M. Lua'i [a,*], Khawla A. Kasar [b], Marwa A. Hassan [c]

[a] Department of Chemistry, College of Sciences, Al- Nahrain University, Baghdad, Iraq.
[b] Applied pathological Analysis department, College of Sciences, Al- Nahrain University, Baghdad, Iraq.
[c] Department of Medical Physics, College of Sciences, Al- Nahrain University, Baghdad, Iraq

ABSTRACT

Breast cancer (BC) remains one of the most common malignancies in women, with its development strongly influenced by hormonal and growth factor signaling. The insulin-like growth factor 1 (IGF1) and its receptor (IGF1-R) are increasingly recognized as key contributors to breast carcinogenesis, particularly in relation to estrogen receptor (ER) status. This study aimed to evaluate circulating IGF1 and IGF1-R levels among Iraqi women with BC and to explore their diagnostic and biological relevance. A total of 90 participants were enrolled, including 65 patients with histologically confirmed BC (41 ER-positive and 24 ER-negative) and 25 healthy controls. Serum concentrations of IGF1 and IGF1-R were measured using ELISA, and statistical analyses were performed with ANOVA, correlation testing, and receiver operating characteristic (ROC) curve assessment. The results demonstrated that both IGF1 and IGF1-R levels were significantly elevated in ER-positive BC patients compared to ER-negative BC patients and healthy controls, whereas no significant differences were observed between ER-negative cases and controls. ROC analysis confirmed the discriminatory potential of these biomarkers, with IGF1 achieving an AUC of 0.8679 when distinguishing ER-positive from ER-negative tumors, while IGF1-R exhibited high specificity (97.44%) at optimal cut-off values. Moreover, a moderate positive correlation was observed between IGF1 and IGF1-R in ER-positive patients, suggesting coordinated regulation within this subgroup. These findings highlight the subtype-specific role of the IGF axis in BC and support the potential clinical utility of IGF1 and IGF1-R as diagnostic indicators and risk-related factors for ER-positive BC. Elevated IGF1 and IGF1-R levels, were observed even in stage I cases, indicating their potential as early biomarkers that could complement mammography in the detection of ER-positive BC.

Keywords: Breast cancer, IGF1, IGF1-R, Estrogen receptors, Early detection

1. Introduction

Breast cancer (BC) represents one of the most prevalent malignancies among women; BC ranks second in mortality. According to the WHO/International Agency for Research on Cancer (IARC), in 2022, there were 2,296,840 cases of BC in the world. BC ranks second after lung cancer as the most prevalent cancer in the world and fourth in mortality, with 666,103 deaths. A markedly higher BC incidence was reported in Asia with 985,817 cases (crude rate: 43.4). China ranks first in the world as the country with the highest incidence of BC due to its population density and longer survival, with 357,161 cases (crude rate:

Received 18 September 2025; revised 29 October 2025; accepted 30 October 2025.
Available online 11 November 2025

* Corresponding author.
E-mail addresses: randamohammad234@gmail.com (R. M. Lua'i), khawla.kasar@nahrainuniv.edu.iq (K. A. Kasar), marwa@nahrainuniv.edu.iq (M. A. Hassan).

https://doi.org/10.70645/3078-3437.1050

51.7). Followed by America, which has 274,375 cases (crude rate: 162.2), and India, with 192,020 cases (crude rate: 28.4) [1].

Although the exact reason for cancers is still a mystery, there are a number of recognized risk factors that increase the likelihood of BC developing. BC risk factors are divided into two categories: modifiable or lifestyle-related risk factors, which are preventable, and non-modifiable risk factors, which cannot be avoided [2]. Modifiable factors include taking hormonal therapy, body mass index (obesity), chemical usage, physical inactivity, smoking and alcohol consumption, consuming processed food, being exposed to artificial light, and insufficient vitamin supplementation. non-modifiable factors such as reproductive history, female sex, familial history, older age, and genetic mutations specifically in BRCA1/2 gene [3].

Currently, the best course of BC treatment is determined based on the molecular subtype of the tumor, which is classified according to specific biomarkers [4]. Among the most frequently assessed biomarkers in BC are those related to hormone stats, as breast tissue is influenced by hormonal signals. These include estrogen or oestrogen receptors (ER) [5], progesterone receptors (PR) [6], and the human epidermal growth factor receptor 2 (HER2) [7]. The status of these receptors, whether positive or negative, can serve as a key determinant in guiding the selection of appropriate therapeutic strategies [8]. Among the most important molecular markers used in the classification of BC is the ER, which serves as both a prognostic and predictive factor. ER-positive tumors often respond well to endocrine therapy, while ER-negative tumors are typically more aggressive and have fewer targeted treatment options [9].

Sex steroid hormones, especially oestrogen, play a very important role in the development of BC cells and can serve as a critical key in the therapeutic response of BC [10]. The biological effects of oestrogen are mediated through binding to its receptors, mainly estrogen receptor alpha (ERα) and beta (ERβ), which upon activation act as transcription factors to regulate gene expression [11], leading to transcriptional activation of genes involved in proliferation and cell survival, oestrogen also engages non-genomic signaling pathways: interaction with membrane-associated receptors, activation of PI3K/AKT and MAPK cascades [12, 13], and modulation of transcription factors such as hypoxia-inducible factor 1-alpha (HIF-1α) [14]. Oestrogen metabolism itself can contribute to breast carcinogenesis. Metabolites of oestradiol can form reactive oxygen species (ROS) or DNAadducts that cause mutations or genomic instability. Polymorphisms in enzymes that mediate estrogen metabolism may alter risk, some oestrogen effects occur independently of the classical ER pathways, indicating alternative routes of carcinogenic signaling [15]. Tumors expressing ER may respond directly to oestrogenic stimulation, while ER-negative tumors may be less responsive to some mechanisms yet possibly influenced via indirect or receptor-independent pathways. Elucidating how oestrogen production, receptor status, and downstream signaling interact can advance understanding of tumor heterogeneity and guide tailored therapeutic strategies.

In parallel, the insulin-like growth factor 1 (IGF-1) and its receptor IGF-1R play crucial roles as mediators of oestrogen in the development of the mammary gland during puberty, forming a key mitogenic and anti-apoptotic signaling pathway that is increasingly implicated in BC [16]. The IGF-1 hormone is important for the function of the mammary gland because it connects with the IGF-1 receptor (IGF-1R), aided by insulin-like growth factor binding proteins (IGFBPs) [17]. Although considerable research has been dedicated to understanding the IGF axis, the precise molecular mechanisms by which IGF-1 contributes to BC remain incompletely defined. New research highlights the important role of IGF-1 and its different forms in starting, advancing, and metastasizing BC [17–19].

Multiple studies have employed genomic, gene activity, and immunohistochemical analyses to investigate the expression of IGF pathway components in BC and their relationship with clinical outcomes [17, 20, 21]. IGF-1R is usually present in higher concentrations in BC cells [22], particularly in luminal A and B types, while lower levels are found in HER2-positive and triple-negative types. This pattern is thought to be modulated by ER activity, which may regulate IGF-1R transcription [21], Higher IGF-1R levels are associated with favorable outcomes, except in HER2- subtypes; elevated IGF-1R expression correlates with poorer prognosis [23]. Several recent studies have examined the relationship between the insulin-like growth factor axis and BC, with a particular focus on ER+ subtypes. Together, these studies highlight the functional and clinical relevance of IGF-1 and its receptor (IGF-1R) in hormone-driven tumor biology. Kruger et al. demonstrated that activation of IGF-1R undermines the efficacy of tamoxifen in ER+ BC. Through analyses of tumor tissues and ER+ cell lines, the study showed that IGF-1R signaling supports cell survival pathways that diminish endocrine therapy response. Their findings suggest that crosstalk between IGF-1R and ER signaling may play a critical role in treatment resistance [24]. Circulating IGF1 and IGF1-R have emerged as promising, biologically plausible biomarkers for identifying estrogen

receptor–positive (ER+) breast cancer because they capture a pathway that is functionally coupled to ER signaling and tumor proliferation. Recent reviews and experimental studies reinforce the crosstalk between estrogen/ER and IGF signaling, document IGF-axis upregulation in luminal subtypes, and report that IGF-1R pathway activity can modulate endocrine therapy response—together providing both pathophysiologic rationale and precedent for biomarker development [25–28].

In a subsequent review, Ianza et al. summarized experimental and clinical evidence linking IGF-1 activity with ER signaling. The review shows that IGF-1 and IGF-1R act synergistically with estrogen to drive tumor proliferation and survival. The authors also highlighted the therapeutic implications, suggesting that targeting IGF-1R could improve outcomes in patients with ER+ BC [29].

The primary aim of this study was to investigate whether elevated serum levels of IGF1 and IGF1-R, measured by ELISA, could serve not only as diagnostic markers but also as potential risk factors for ER+ BC. A further objective was to assess their value in early-stage patients and explore the possibility of integrating these parameters with mammography to enhance early detection of ER+ BC, the most common molecular subtype.

2. Materials and methods

2.1. Study design and setting

Patient samples were collected from the Oncology Teaching Hospital in Baghdad, Iraq, while control samples were obtained from clinically healthy women with no history of malignancy during December 2024–June 2025. Exclusion criteria included patients with primary cancers that metastasized to the breast from other organs, liver diseases, chronic diseases such as diabetes and high blood pressure, polycystic ovary syndrome, and breastfeeding women.

2.2. Participants and sample collection

In this study, 5 ml of peripheral blood was sampled from each female enrolled, a total of 90 Iraqi females, including 65 diagnosed with BC at various stages and 25 healthy subjects. The age of participants was 20–70 years. We divided the patients into 2 groups based on their ER status. The first cohort comprised 41 BC patients with estrogen receptor–positive (ER+) tumors, representing cases characterized by hormonal receptor expression. The second cohort included 24 BC patients with estrogen receptor–negative (ER−) tumors, representing cases lacking such receptor expression. This grouping enabled a systematic evaluation of IGF1 and IGF1-R levels across healthy subjects and BC patients with different ER statuses.

2.3. Parameter analysis

Similarly, we collected blood samples under standardized conditions. The insulin-like growth factor 1 (IGF-1) and its receptor (IGF-1R) were measured from serum samples.

The biochemical analyses of IGF1 and IGF1-R were performed using commercial enzyme-linked immunosorbent assay (ELISA) kits (Nanhu Dist, Jiaxing, China). following the manufacturers' operating manuals. The resulting optical density (OD) was measured via a microplate Human Reader ELISA (manufactured in Germany) at a specific wavelength, ensuring accurate results.

2.4. Statistical analysis

The data were analyzed using GraphPad Prism 9.3 Statistics software. One-way analysis of variance (ANOVA) was employed to compare parameter levels, including IGF1 and IGF1-R. We conducted a correlation analysis to evaluate correlations between parameter levels in BC groups. The ROC curve was used twice: initially to determine the optimal cut-off and diagnostic accuracy by comparing healthy controls with all BC patients, and subsequently to differentiate between patients with ER-positive and ER-negative tumors. for Statistical significance was set at $P < .05$.

2.5. Ethical approval

This study was approved by the Research Ethics Committee of the College of Science, Al-Nahrain University, Baghdad, Iraq (Approval No. 1\8-RECSNU) on 2/6/2025. All procedures involving human samples were conducted in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration.

3. Results

The demographic characteristics of the patient samples in Table 1 revealed 2 groups of BC patients: BC patients with estrogen receptor–positive (ER+) tumors and BC patients with estrogen receptor–negative (ER−) tumors Most patients were under 50 years old, and most patients received chemotherapy. Additionally, the number of patients with cancer

Table 1. Demographic characteristics of the BC patients.

Variable	Frequency (%)
Diagnosis Age Group (years)	
Under-50	36 (55.38)
50 +	29 (44.61)
Chemotherapy	
Yes	45 (69)
No	20 (31)
Surgery	
Yes	45 (69)
No	20 (31)
Hormone Therapy	
Yes	45 (69)
No	20 (31)
Stage	
I	16 (25)
II	20 (31)
III	14 (21)
IV	15 (23)
Cancer Subtypes	
Luminal A	30 (46)
Luminal B	13 (20)
Her-2 Positive	12 (19)
Triple negative	10 (15)
Hormone Receptors state	
ER +	41 (61)
ER–	24 (34)
PR +	37 (59)
PR–	23 (35)

in the right breast was 37, while 28 patients had cancer in the left breast.

The comparative analysis of circulating IGF1 and IGF1-R levels is listed in Table 2 and Fig. 1. Mean serum IGF1 concentration was significantly elevated

Table 2. Serum levels of IGF1 and IGF1-R in the studied BC patients and control.

Parameter	Groups	Mean ± SD	P-value
IGF1	Control	15.63 ± 1.617	< 0.0001[a]
	ER + Group	18.39 ± 2.481	0.7016[b]
	ER– Group	15.15 ± 1.803	< 0.0001[c]
IGF1-R	Control	14.36 ± 2.879	0.0076[a]
	ER + Group	17.18 ± 3.534	0.9806[b]
	ER– Group	14.17 ± 4.227	0.0047[c]

[a] adjusted P-value of control group vs patients with ER + ;
[b] adjusted P-value of control group vs patients with ER–;
[c] adjusted P-value of patients with ER + vs patients with ER–.

in ER + patients (18.39 ± 2.48 ng/mL) compared to both controls (15.63 ± 1.62 ng/mL, $P < 0.0001$) and ER- patients (15.15 ± 1.80 ng/mL, $P < 0.0001$). In contrast, no significant difference was observed between the control and ER– groups ($P = 0.7016$).

Similarly, IGF1-R levels were significantly higher in patients with ER + (17.18 ± 3.53 ng/mL) than in controls (14.36 ± 2.87 ng/mL, $P = 0.0076$) and BC patients with ER- (14.17 ± 4.22 ng/mL, $P = 0.0047$). However, there was no statistically significant difference between patients with ER– and controls ($P = 0.9806$).

ROC analysis was performed to evaluate the diagnostic accuracy of IGF1 and IGF1-R. When comparing ER + patients with controls (Table 3, Fig. 2), IGF1 demonstrated an area under the curve (AUC) of 0.7917 (95% CI: 0.6860–0.8974, $P < 0.0001$) with 96% specificity with 56.1% sensitivity at a cutoff value of > 17.53 ng/mL. Similarly, IGF1-R yielded an

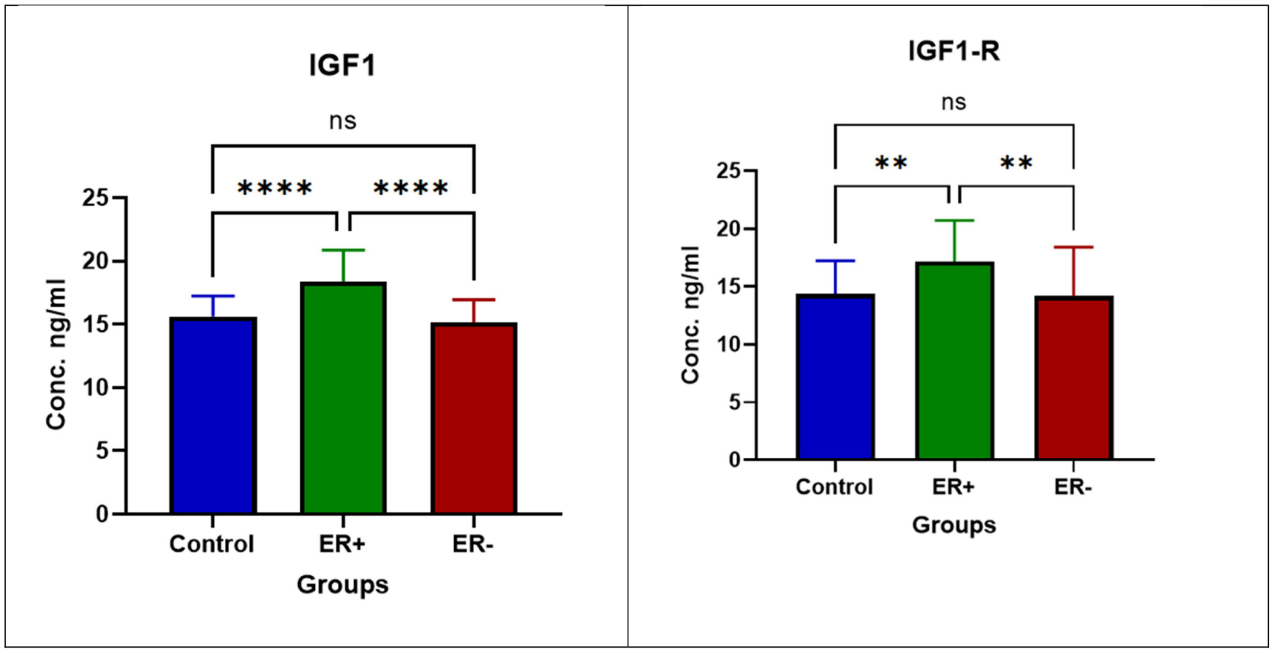

Fig. 1. Serum levels of IGF1 and IGF1-R in the studied BC patients and control.

Table 3. The ROC curve analysis of parameters in control and ER+ patient groups.

Parameters	AUC	Sensitivity%	Specificity%	95% CI	cutoff	P-value
IGF1	0.7917	56.1	96	0.6860–0.8974	>17.53	<0.0001
IGF1-R	0.7333	53.85	96	0.6080–0.8587	>16.40	0.0017

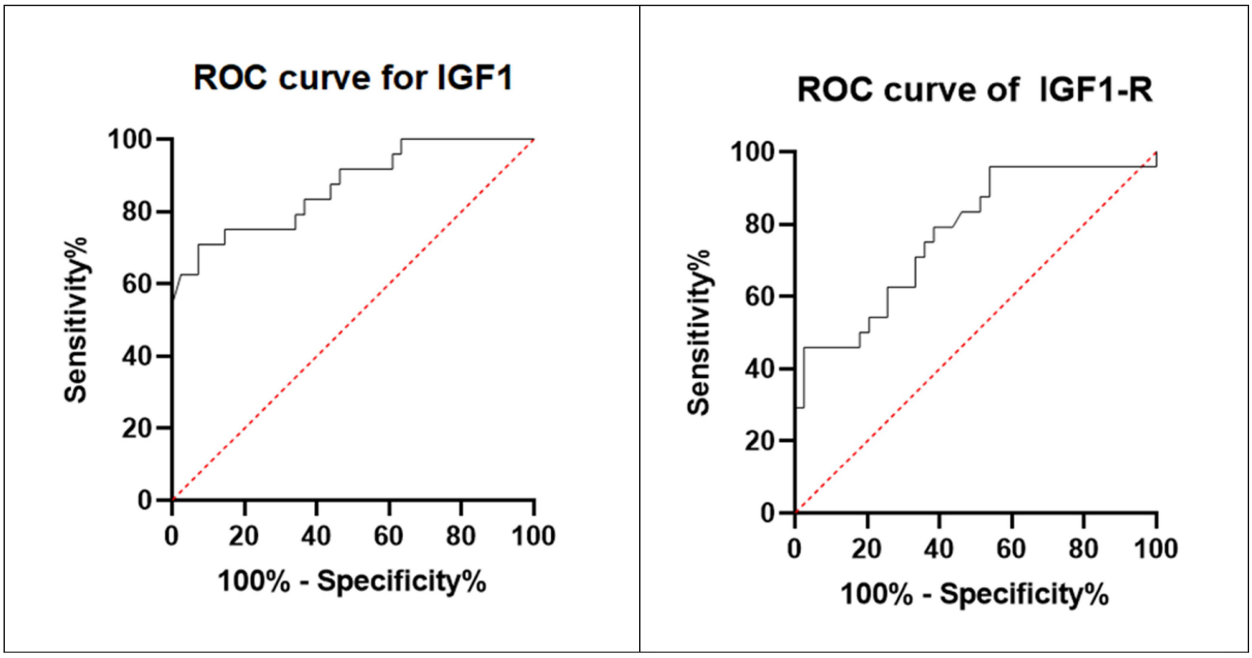

Fig. 2. The ROC curve analysis of parameters in control and ER+ patient groups.

AUC of 0.7333 (95% CI: 0.6080–0.8587, P = 0.0017), achieving 96% specificity with 53.85% sensitivity at a cutoff of >16.40 ng/mL.

In the comparison between ER+ and ER- groups (Table 4, Fig. 3), IGF1 showed excellent discriminatory capacity with an AUC of 0.8679 (95% CI: 0.7744–0.9614, P < 0.0001). At a cutoff of <15.47 ng/mL, the specificity was 92.68% with a sensitivity of 70.83%. For IGF1-R, the AUC was 0.7730 (95% CI: 0.6517–0.8943, P= 0.0003), with 97.44% specificity and 45.83% sensitivity at a cutoff <12.86 ng/mL.

Correlation patterns between IGF1 and IGF1-R are detailed in Table 5. In the ER+ group, IGF1 and IGF1-R demonstrated a good positive correlation (r = 0.5302, P = 0.0004), with an R^2 value of 0.2811, indicating that approximately 28% of the variability in IGF1-R could be explained by IGF1 levels (Fig. 4). Conversely, in the ER group, the correlation between IGF1 and IGF1-R was weak and statistically nonsignificant (r = 0.2463, P = 0.2459).

4. Discussion

This study was designed to test the hypothesis that elevated IGF1 and IGF1-R concentrations are not merely markers of disease but may contribute causally to the development of estrogen receptor–positive (ER+) BC. In the present study (65 BC patients and 25 healthy controls; ER+ n = 41, ER− n = 24), mean serum IGF1 and IGF1-R were consistently and substantially higher in ER+ patients than in both healthy controls and ER− cases (Table 2). Specifically, mean IGF1 was 18.39 ± 2.48 ng/mL in ER+ patients versus 15.63 ± 1.62 ng/mL in controls and 15.15 ± 1.80 ng/mL in ER− patients (adjusted

Table 4. The ROC curve analysis of parameters in patient groups.

Parameters	AUC	Sensitivity%	Specificity%	95% CI	cutoff	P-value
IGF1	0.8679	70.83	92.68	0.7744–0.9614	<15.47	<0.0001
IGF1-R	0.7730	45.83	97.44	0.6517–0.8943	<12.86	0.0003

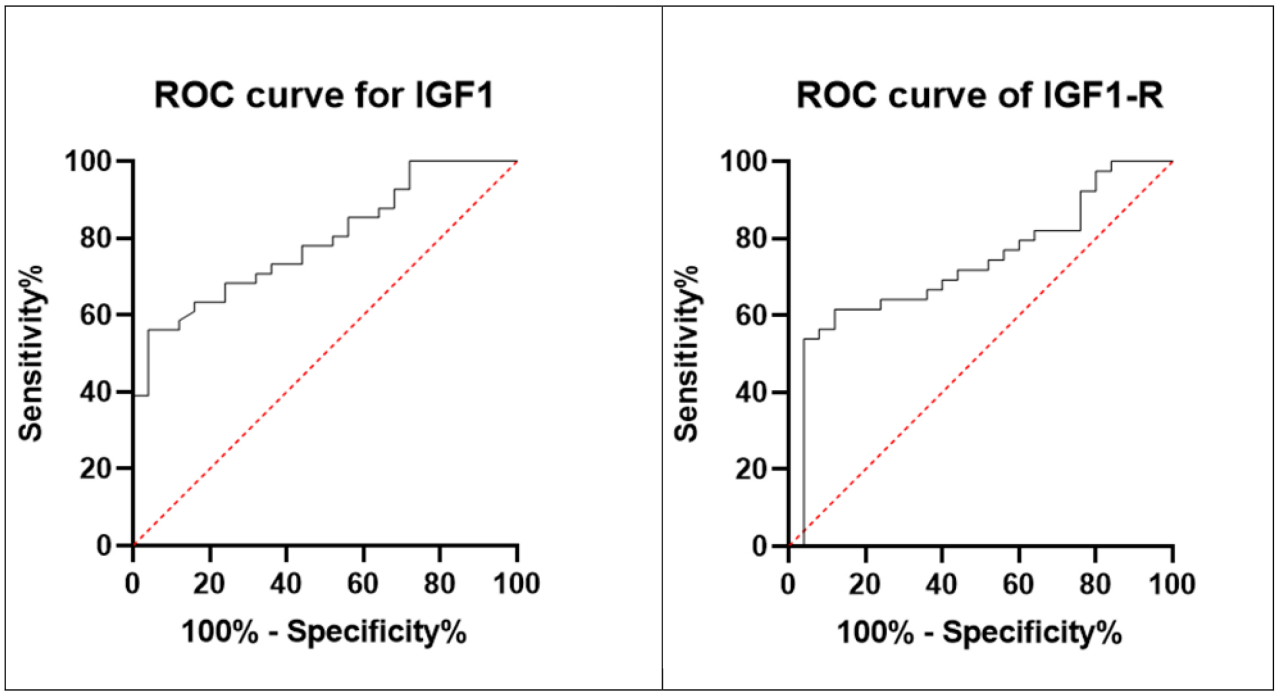

Fig. 3. The ROC curve analysis of parameters in patient groups.

Table 5. The correlation analysis of parameters in patient groups.

Pearson r	IGF1-R vs. IGF1in ER+	IGF1-R vs. IGF1in ER–
r	0.5302	0.2463
95% confidence interval	0.2659 to 0.7204	–0.1744 to 0.5910
R squared	0.2811	0.06068
P-value	0.0004	0.2459

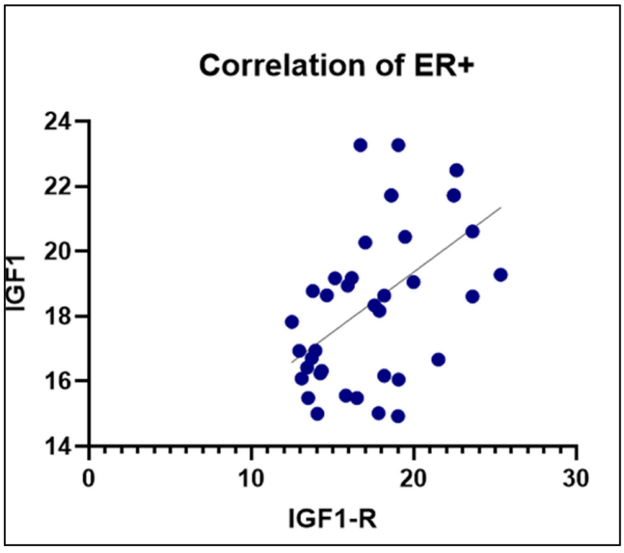

Fig. 4. The correlation analysis of parameters in patient groups.

$p < 0.0001$ for ER+ vs. control and ER+ vs. ER−; control vs. ER−, $p = 0.7016$). Mean IGF1-R followed the same subtype-specific pattern (ER+ 17.18 ± 3.53 ng/mL; control 14.36 ± 2.88 ng/mL; ER− 14.17 ± 4.23 ng/mL; adjusted $p = 0.0076$ and $p = 0.0047$, respectively). These quantitative differences provide the empirical foundation for examining causality.

This result supports a model in which estrogen signaling and the IGF axis are functionally coupled in luminal BC. ER activity modulates transcriptional networks that regulate IGF pathway components, and conversely IGF signaling amplifies ER-driven mitogenic programs through PI3K/AKT and MAPK cascades; this bidirectional crosstalk can boost proliferation and survival in ER+ tumors and plausibly explains why IGF1 and IGF1-R are concurrently elevated in ER-positive tumors [30]. The observed absence of significant differences between controls and ER- patients for both analytes suggests that upregulation of the IGF axis is not a universal feature of all BC subtypes but is concentrated in hormone-receptor–positive biology. This subtype specificity parallels prior observations that IGF1R expression and IGF signaling show differential distribution and prognostic associations across BC subtypes—with IGF pathway activity often more prominent or functionally relevant in luminal tumors than in many HER2-positive or triple-negative cases [31].

Epidemiologic data linking higher IGF1 concentration to increased cancer risk provide population-level plausibility for the findings: elevated systemic IGF1 has been associated with greater incidence of several

cancers, including BC, in large cohorts. In that light, the higher mean IGF1 among ER+ patients (18.39 ng/mL) compared with controls (15.63 ng/mL) and ER− patients (15.15 ng/mL) is consistent with both tumor-intrinsic upregulation and host exposure patterns that may predispose specifically to ER-driven tumorigenesis [32]. The absolute difference in mean IGF1 between ER+ patients (18.39 ± 2.48) and controls (15.63 ± 1.62)—approximately 2.8 ng/mL—was statistically robust ($p < 0.0001$). Given the SD values, this difference reflects a large standardized effect and is unlikely to be explained by random sampling alone. The parallel pattern for IGF1-R (ER+ 17.18 ± 3.53 vs. control 14.36 ± 2.88; $p = 0.0076$) reinforces that both ligand and receptor are increased in ER+ disease. In contrast, nonsignificant comparisons between control and ER− groups for IGF1 ($p = 0.7016$) and IGF1-R ($p = 0.9806$) indicate that ER− tumors in this study do not show systemic IGF axis perturbation detectable by serum ELISA. A large prospective investigation within the EPIC cohort examined circulating IGF-I concentrations in relation to subsequent BC risk. The analysis, which included 938 incident BC cases and 1,394 matched controls, found that women with higher pre-diagnostic IGF-I levels had an elevated risk of developing hormone receptor–positive tumors, particularly among those diagnosed after the age of 50. The association was not evident for ER-negative BC. These findings suggest that increased circulating IGF-I may act as a risk factor specifically for ER-positive BC, supporting a role for IGF signaling in hormonally driven carcinogenesis [33]. Another study evaluated expression of IGF1R protein by immunohistochemistry in invasive BC specimens and examined its association with various molecular markers, including hormone receptors. Among the study, about half (50%) of tumors showed strong IGF1R expression. A statistically significant correlation was observed between strong expression of IGF1R and expression of the vitamin D receptor (VDR), which itself shows variation among molecular subtypes. Although the study did not exclusively focus on ER positivity vs negativity in all analyses, many of the tumors with high IGF1R expression also exhibited positive hormone receptor status. The findings suggest that IGF1R overexpression is common in breast cancers with hormone receptor expression, supporting the idea that IGF1R could contribute to risk or progression in ER-positive disease [34].

In the present study, a considerable proportion of the included BC cases were classified as stage I, reflecting an early phase of BC. Notably, elevated serum concentrations of IGF1 and IGF1-R were consistently observed in these patients, particularly among those with ER-positive tumors. This finding suggests that aberrant activation of the IGF axis may occur at an early stage of tumor development and could therefore serve as a valuable tool for the early detection of ER-positive BC. Given that this molecular subtype represents the most prevalent form of BC worldwide, the ability to identify parameter changes at early stages highlights the potential clinical utility of IGF1 and IGF1-R as complementary tools for early screening and timely intervention. Importantly, such molecular indicators could be integrated with mammography to enhance the sensitivity and specificity of early diagnostic strategies, providing a complementary bioengineering approach that supports precision screening and improves clinical decision-making in ER-positive BC.

The ROC analyses presented in this study provide compelling evidence that elevated levels of IGF1 and IGF1-R may not only serve as diagnostic indicators but also represent potential risk factors for the development of ER+ BC. The ability of these parameters to distinguish ER+ cases from both healthy controls and ER− patients highlights their biological and clinical relevance. When ER+ patients were compared with healthy individuals, IGF1 demonstrated good discriminatory ability with an AUC of 0.7917. At a threshold of 17.53 ng/mL, specificity reached 96%, indicating that values above this cutoff are rarely found in cancer-free women, while sensitivity was 56.1%. A similar pattern was observed for IGF1-R, which achieved an AUC of 0.7333 and the same high specificity at a threshold of 16.40 ng/mL. These results suggest that markedly elevated concentrations of either marker are strongly associated with ER+ BC and are unlikely to occur in healthy subjects, supporting the view that such elevations may contribute to the underlying risk landscape.

The comparison between ER+ and ER− tumors further strengthens this interpretation. IGF1 reached an excellent AUC of 0.8679, with a sensitivity of 70.83% and a specificity of 92.68% at a cutoff of 15.47 ng/mL. This superior performance implies that IGF1 elevation is more closely tied to the ER+ BC than to BC in general, pointing toward a mechanistic role in hormone-driven tumorigenesis. IGF1-R, while showing lower sensitivity (45.83%), provided the highest specificity of 97.44% at a cutoff of 12.86 ng/mL, indicating that patients with values exceeding this threshold are highly likely to harbor ER+ tumors. The extremely high specificity of both markers at their optimal cutoffs reduces the probability that such elevations are incidental, reinforcing their interpretation as potential risk factors rather than secondary consequences.

From a clinical and biological standpoint, these results are significant. High specificity coupled with

substantial effect sizes suggests that abnormal increases in IGF1 and IGF1-R are not simply diagnostic correlates but may reflect a pathogenic environment that predisposes to ER+ tumor initiation. The well-established crosstalk between the IGF axis and ER signaling provides a mechanistic framework: IGF1 promotes receptor activation and downstream proliferative signaling, while estrogen can upregulate IGF1-R expression. This bidirectional amplification loop may explain why women with elevated levels of these parameters are more susceptible to developing ER+ disease.

Although the present findings are cross-sectional, the strength and direction of the associations, particularly the large AUC values and high likelihood ratios, suggest that increased IGF1 and IGF1-R represent more than coincidental markers. Instead, they may function as biologically meaningful risk factors whose elevation creates a favorable milieu for estrogen-dependent carcinogenesis. Larger prospective studies and genetic analyses will be required to definitively establish temporality and causality, but the evidence here supports the hypothesis that heightened IGF signaling contributes to susceptibility to ER+ BC.

The correlation analysis presented in Table 5 provides important insights into the relationship between serum IGF1 and IGF1-R concentrations across different breast cancer subgroups. In ER+ patients, the analysis revealed a statistically significant moderate positive correlation ($r = 0.5302$, $P = 0.0004$), with an R^2 value of 0.2811. This indicates that nearly 28% of the variability in IGF1-R levels can be attributed to changes in IGF1 concentrations. The strength and significance of this correlation strongly suggest a coordinated regulation of ligand and receptor within the IGF axis in ER+ tumors. Mechanistically, this aligns with the well-documented crosstalk between estrogen signaling and IGF1 pathways, where estrogen enhances IGF1-R expression and IGF1, in turn, amplifies estrogen-driven mitogenic signals. Such coupling may create a synergistic proliferative environment that fosters tumor progression in ER+ BC.

In contrast, the ER− group demonstrated only a weak and statistically nonsignificant correlation between IGF1 and IGF1-R ($r = 0.2463$, $P = 0.2459$, $R^2 = 0.06068$). The negligible explanatory power of IGF1 over IGF1-R variability in this group suggests that the IGF signaling axis operates largely independently of receptor-ligand co-regulation in the absence of ER activity. This finding underscores the biological heterogeneity of BC, indicating that IGF signaling may not be uniformly relevant across molecular subtypes. Rather, its functional integration appears to be subtype-specific, with greater pathophysiological importance in hormonally driven tumor.

In summary, Serum IGF1 and IGF1-R levels were significantly higher in ER+ BC patients compared with ER− patients and healthy controls, indicating their association with hormonal receptor status, as they reflect a pathway that is functionally coupled to ER signaling and tumor proliferation. In the present cohort, both parameters were significantly higher in ER+ than in ER− patients and healthy controls, and IGF1 demonstrated excellent discrimination (AUC = 0.8679), while IGF1-R provided very high specificity (97.44%), supporting their potential utility for subtype-specific detection rather than universal breast cancer screening. Importantly, our cohort included ER+ patients at stage I, in whom both IGF1 and IGF1-R concentrations were already elevated, indicating that activation of the IGF axis occurs early in tumor development. These findings are consistent with recent studies (Kumar & Chaudhri; Salah et al.; Soni et al.) [18, 19, 21] that have highlighted the strong crosstalk between estrogen and IGF-1R signaling, the overexpression of IGF-axis components in luminal subtypes, and their contribution to endocrine therapy resistance. Such results provide both a biological rationale and epidemiologic support for considering IGF1 and IGF1-R as early diagnostic and risk-related indicators in ER+ breast cancer. However, further prospective investigations with standardized assays and larger cohorts are still required to confirm their diagnostic accuracy and to establish clinical cut-off values for early detection applications. Clinically, these differential correlation patterns suggest that therapeutic strategies targeting the IGF axis may hold greater promise in ER+ subtypes, where the receptor-ligand relationship is functionally relevant. Future research should validate these findings in a larger sample size and investigate whether dual inhibition of ER and IGF signaling produces additive or synergistic benefits in patients with ER+ BC. Future studies should involve a greater number of patients and healthy controls to strengthen the statistical power, confirm reproducibility, and enhance the generalizability of the findings.

5. Conclusion

This study demonstrated that serum IGF1 and IGF1-R levels are significantly elevated in ER+ BC patients compared to ER− patients and healthy controls. The strong discriminatory performance of these parameters, particularly IGF1, underscores their potential role as risk-related factors rather than incidental

findings. The observed positive correlation between IGF1 and IGF1-R in ER+ patients further support the hypothesis of a coordinated signaling axis that may contribute to hormone-driven carcinogenesis. Collectively, these findings highlight the clinical and biological importance of the IGF pathway in ER+ BC and suggest that abnormal elevations in IGF1 and IGF1-R could represent meaningful contributors to disease susceptibility. Our findings suggest that elevated IGF1 and IGF1-R, detectable even in stage I patients, could be integrated with mammography to strengthen early diagnostic strategies for ER-positive BC.

Acknowledgement

The authors would like to express their sincere gratitude to the College of Science/Al-Nahrain University for providing the academic support to complete this work.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. "Global Cancer Observatory," International Agency for Research on Cancer, Lyon, France. ps://gco.iarc.fr/(accessed 2025).
2. B. Smolarz, A. Z. Nowak, and H. Romanowicz, "Breast Cancer—Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature)," *Cancers*, vol. 14, no. 10, p. 2569, 2022.
3. S. Łukasiewicz, M. Czeczelewski, A. Forma, J. Baj, R. Sitarz, and A. Stanisławek, "Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review," *Cancers,* vol. 13, no. 17, p. 4287, 2021.
4. P. Gamble *et al.*, "Determining breast cancer biomarker status and associated morphological features using deep learning," *Commun. Med.,* vol. 1, no. 1, p. 14, 2021.
5. P. Miziak *et al.*, "Estrogen receptor signaling in breast cancer," *Cancers (Basel),* vol. 15, no. 19, p. 4689, 2023.
6. Z. Li, H. Wei, S. Li, P. Wu, and X. Mao, "The role of progesterone receptors in breast cancer," *Drug Des. Devel. Ther.,* pp. 305–314, 2022.
7. A. M. Elshazly and D. A. Gewirtz, "An overview of resistance to Human epidermal growth factor receptor 2 (Her2) targeted therapies in breast cancer," *Cancer Drug Resistance,* vol. 5, no. 2, p. 472, 2022.
8. A. N. Cobb, R. Czaja, J. Jorns, and C. S. Cortina, "Breast Cancer Subtypes: Clinicopathologic Features and Treatment Considerations," *Curr. Breast Cancer Rep.,* vol. 16, no. 2, pp. 150–160, 2024.
9. G. Qi, X. Zhang, X. Gai, and X. Yan, "Retrospective analysis of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), Ki67 changes and their clinical significance between primary breast cancer and metastatic tumors," *PeerJ,* vol. 12, p. e17377, 2024.
10. E. P. Hamilton *et al.*, "ARV-471, an estrogen receptor (ER) PROTAC degrader, combined with palbociclib in advanced ER+/human epidermal growth factor receptor 2–negative (HER2-) breast cancer: Phase 1b cohort (part C) of a phase 1/2 study," ed: American Society of Clinical Oncology, 2022.
11. L. Clusan, F. Ferrière, G. Flouriot, and F. Pakdel, "A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer," *Int. J. Mol. Sci.,* vol. 24, no. 7, p. 6834, 2023.
12. M. S. Hassan, C. Johnson, S. Ponna, D. Scofield, N. Awasthi, and U. von Holzen, "Inhibition of insulin-like growth factor 1 receptor/insulin receptor signaling by small-molecule inhibitor BMS-754807 leads to improved survival in experimental esophageal adenocarcinoma," *Cancers (Basel),* vol. 16, no. 18, p. 3175, 2024.
13. Z. Zhang, A. Richmond, and C. Yan, "Immunomodulatory properties of PI3K/AKT/mTOR and MAPK/MEK/ERK inhibition augment response to immune checkpoint blockade in melanoma and triple-negative breast cancer," *Int. J. Mol. Sci.,* vol. 23, no. 13, p. 7353, 2022.
14. M. Valko-Rokytovská, P. Očenáš, A. Salayová, and Z. Kostecká, "Breast cancer: targeting of steroid hormones in cancerogenesis and diagnostics," *Int. J. Mol. Sci.,* vol. 22, no. 11, p. 5878, 2021.
15. M. Oshi *et al.*, "Abundance of reactive oxygen species (ROS) is associated with tumor aggressiveness, immune response, and worse survival in breast cancer," *Breast Cancer Res. Treat.,* vol. 194, no. 2, pp. 231–241, 2022.
16. D. Pellacani, S. Tan, S. Lefort, and C. J. Eaves, "Transcriptional regulation of normal human mammary cell heterogeneity and its perturbation in breast cancer," *EMBO,* vol. 38, no. 14, p. e100330, 2019.
17. S. A. Sadighi, N. Rostami, M. Tohidi, and M. Mashayekhi, "Insulin-like growth factor (IGF) levels in pre-treatment plasma identifying breast cancer: A case control study," *Caspian Journal of Internal Medicine,* vol. 15, no. 4, p. 706, 2024.
18. S. Kumar and S. Chaudhri, "Recent update on IGF-1/IGF-1R signaling axis as a promising therapeutic target for triple-negative breast cancer," *Pathology-Research and Practice,* vol. 263, p. 155620, 2024.
19. H. Salah *et al.*, "Targeting insulin-like growth factor-1 (IGF-1) by using metformin in non-diabetic metastatic breast cancer female patients: a randomized controlled trial," *Cancer Chemother. Pharmacol.,* vol. 95, no. 1, pp. 1–9, 2025.
20. O. T. Cox, S. O'Shea, E. Tresse, M. Bustamante-Garrido, R. Kiran-Deevi, and R. O'Connor, "IGF-1 receptor and adhesion signaling: an important axis in determining cancer cell phenotype and therapy resistance," *Front. Endocrinol. (Lausanne),* vol. 6, p. 106, 2015.
21. U. K. Soni, L. Jenny, and R. S. Hegde, "IGF-1R targeting in cancer–does sub-cellular localization matter?," *J. Exp. Clin. Cancer Res.,* vol. 42, no. 1, p. 273, 2023.
22. E. Acosta-Ramos, M. Segovia-Mendoza, and J. A. Olivares-Reyes, "Growth Factor Receptor Implications in Breast Cancer: Prospects for Their Molecular Transactivation in the Future and Obstacles for Target Therapy," in *Breast Cancer*

Treatment: An Interdisciplinary Approach: Springer, 2024, pp. 237–301.
23. S. Roche *et al.*, "Preclinical evaluation of Insulin-like growth factor receptor 1 (IGF1R) and Insulin Receptor (IR) as a therapeutic targets in triple negative breast cancer," *PLoS One,* vol. 18, no. 3, p. e0282512, 2023.
24. D. T. Kruger *et al.*, "IGF-1R pathway activation as putative biomarker for linsitinib therapy to revert tamoxifen resistance in ER-positive breast cancer," *Int. J. Cancer,* vol. 146, no. 8, pp. 2348–2359, 2020.
25. A. Kotsifaki, S. Maroulaki, E. Karalexis, M. Stathaki, and A. Armakolas, "Decoding the Role of Insulin-like Growth Factor 1 and Its Isoforms in Breast Cancer," *Int. J. Mol. Sci.,* vol. 25, no. 17, p. 9302, 2024.
26. E. F. Petricoin *et al.*, "Immune and Growth Factor Signaling Pathways Are Associated with Pathologic Complete Response to an Anti–Type I Insulin-like Growth Factor Receptor Regimen in Patients with Breast Cancer," *Clinical Cancer Research,* vol. 31, no. 20, pp. 4361–4371, 2025.
27. C. A. Galifi *et al.*, "Insulin-Like Growth Factor 1 Receptor Regulates Breast Cancer Cell Adhesion through Beta-1 Integrin," *bioRxiv,* p. 2025.09. 11.674989, 2025.
28. V. Gentilini *et al.*, "Glucose-dependent insulin-like growth factor 1 secretion promotes breast cancer cell tumorigenesis," *Life Sci.,* p. 124020, 2025.
29. A. Ianza, M. Sirico, O. Bernocchi, and D. Generali, "Role of the IGF-1 axis in overcoming resistance in breast cancer," *Frontiers in cell and developmental biology,* vol. 9, p. 641449, 2021.
30. F. Silva Rocha, J. H. da Silva Maues, C. M. Brito Lins Pereira, C. A. Moreira-Nunes, and R. M. Rodriguez Burbano, "Analysis of increased egfr and igf-1r signaling and its correlation with socio-epidemiological features and biological profile in breast cancer patients: A study in northern Brazil," *Breast Cancer (London)*, pp. 325–339, 2021.
31. Y.-T. Chan *et al.*, "The interplay between IGF-1R signaling and Hippo-YAP in breast cancer stem cells," *Cell Communication and Signaling,* vol. 21, no. 1, p. 81, 2023.
32. F. Qian and D. Huo, "Circulating insulin-like growth factor-1 and risk of total and 19 site-specific cancers: cohort study analyses from the UK biobank," *Cancer Epidemiol. Biomarkers Prev.,* vol. 29, no. 11, pp. 2332–2342, 2020.
33. R. Kaaks *et al.*, "Insulin-like growth factor I and risk of breast cancer by age and hormone receptor status—A prospective study within the EPIC cohort," *Int. J. Cancer,* vol. 134, no. 11, pp. 2683–2690, 2014.
34. A. Alnimer *et al.*, "Association between expression of vitamin D receptor and insulin-like growth factor 1 receptor among breast cancer patients," *World J. Oncol.,* vol. 14, no. 1, p. 67, 2023.