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Assessment of Hormonal Imbalance and Diagnostic Accuracy with Renal Function Parameters in Women with Breast Cancer: A Correlation Study

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Abstract

Reduced kidney function significantly influences breast cancer (BC) pathophysiology by disrupting hormone metabolism, leading to elevated systemic exposure to endogenous estrogens and their metabolites.

This study aimed to investigate the relationships among estradiol (E2), progesterone (P4), and CA15, as well as renal function parameters (Urea and Creatinine) in women diagnosed with BC.

A total of 160 Iraqi women participated and were categorized into Group A (n = 40, BC with normal renal function), Group B (n = 40, BC with renal dysfunction), and Group C (n = 80, healthy controls). CA15.3 was measured using a Cobas automated analyzer (Roche). Estradiol (E2) and Progesterone (P4) levels were determined using ELISA kits provided by BioCompare. Urea and Creatinine (Cr) were determined using spectrophotometric techniques.

The findings revealed statistically significant differences ($P < 0.001$) in E2, P4, Cr, urea, and CA15.3 between the patient and healthy groups. CA15.3, E2, and P4 demonstrated the highest discriminative ability ($P<0.001$), whereas Cr showed the strongest diagnostic performance, with an AUC of 0.868 ($P<0.001$). Pearson correlation analysis revealed that CA15.3 was negatively correlated with both E2 and P4 ($p<0.001$). In addition, a strong negative correlation was observed between Estradiol (E2) and both Urea and Creatinine ($r = -0.5728$, $p<0.001$). Moreover, strong negative correlations were observed between Progesterone (P4) and both Urea and Creatinine ($r = -0.4831$, $r = -0.5212$, $p < 0.001$).

Reduced kidney function establishes a complex, tumor-promoting environment that greatly affects the pathophysiology of BC. The association is fueled by a mix of hormonal imbalance, ongoing inflammation, and modified toxin metabolism, which collectively encourage cancer development and progression.

Keywords: Breast Cancer, Estradiol, Progesterone, Renal Function, CA15.3, Urea.

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Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy and the most common cause of cancer-related mortalities in women globally, making it a significant public health challenge (1).

In hormone-sensitive cases, Estradiol (E2) and Progesterone (P4) are the key propelling agents of tumor proliferation and progression (2). E2 plays a significant role in the growth of hormone receptor-positive (ER+) BC by stimulating cell proliferation. While high endogenous E2 levels are linked to increased risk in postmenopausal women, studies show that estrogen-only therapy carries little to no increased BC risk. In contrast, combined estrogen-progestogen therapy presents a higher risk (3). Like E2, P4 is critical for the expansion of mammary gland progenitor cells and lobuloalveolar development. Progesterone signaling (via PR-B) is linked to breast cancer progression, with some studies suggesting it "tricks" the immune system to allow tumor cells to grow unchecked (4,5).

The risk of BC is significantly influenced by environmental factors, notably the use of progestogens (synthetic progestins) in combination with E2 in menopausal hormone therapy (MHT), which can lead to a 1.14 to 2.38-fold higher risk (6). Accurate monitoring of serum E2 and P4 is essential for optimizing reproductive health outcomes and managing oncological conditions (7,8).

However, the clinical accuracy of these markers is closely related to the body's ability to excrete. Metabolic excretion of steroid hormone metabolites and tumor-associated antigens, such as CA15.3, is therefore the domain of renal clearance (9,10).

Chronic kidney disease (CKD) or a transient period of renal failure will both adversely impact. This process of elimination results in an overall increase in marker levels, which may falsely elevate marker levels, affecting staging (11-13).

In addition, although P4 is beneficial for breast cancer prognosis, as a guide for clinical diagnosis, it relies on stable systemic concentrations maintained by regular renal clearance (14).

Recent evidence using the latest mass spectrometry (UPLC-MS/MS) has shown that P4 and its metabolites are systematically excreted in human urine, suggesting that renal integrity is essential for maintaining a representative profile of circulating hormones (15). Although these hormones play a role clinically, the extent to which certain renal parameters, including Urea and Creatinine, are related to E2 and P4 levels in BC patients is less well documented. Grasping this interplay of biochemical states is critical to distinguishing between true disease progression and renal-mediated delayed metabolic response. This conceptual framework, which shows the association of renal deficit and the systemic rise of biomarkers, is further illustrated in Figure 1. Therefore, this study aims to investigate E2, P4, and CA15. 3 with renal function parameters (Urea and Creatinine) in women with BC.

Materials &Methods

Subjects of study:

A total of one hundred and sixty Iraqi women, 80 patients, and 80 healthy control individuals were enrolled in this study and divided into three primary groups based on their clinical diagnosis and renal function status:

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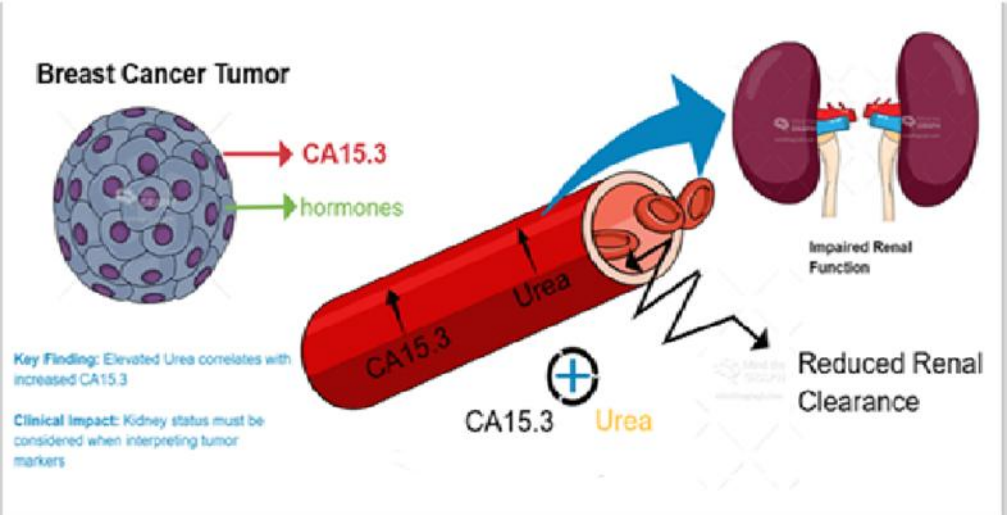

Figure 1: Graphical abstract illustrating the relationship between renal impairment and serum CA15.3 levels in breast cancer patients. (The arrows indicate the metabolic lag and reduced clearance of biomarkers due to elevated Urea levels), created by the author in mindthegraph.com.

Group A consists of 40 women diagnosed with breast cancer and normal renal function parameters (serum Urea and Creatinine within reference ranges). Forty breast cancer patients with renal dysfunction (Group B). Renal dysfunction is classified as elevated serum levels of Urea and Creatinine. Group C consists of 80 apparently healthy non-breast cancer patients with no history of renal disease.

Blood Sample Collection and Preparation

Each subject's venous blood (~5 ml) was drawn using the Gel test tubes. the whole time. (free of anticoagulants) were subsequently used to contain them, then left to coagulate at room temperature for 15-20 min. After centrifugation at 3000 rpm for 10 min, serum was isolated from the clots. Serum was then divided into aliquots and preserved at -20 °C, using the blood units as identification. Based on the group and ID numbers, the samples were given
appropriate serial numbers to ensure the correct measurement of Urea, Creatinine, E2, and P4.

Study Duration

The study was conducted at Al Amal National Cancer Hospital. Data and blood samples from clinical tests were obtained from (15/8/2025) to (20/10/2025). And its methods conformed to ethics standards for research.

Laboratory and Biochemical Analysis

Lab Tests: The laboratory performed precise, reliable analyses of all results using high-quality diagnostic kits from a reputable German enterprise. The serum marker CA 15.3 was measured using the Cobas® Roche Diagnostics system. These tests were performed with Bio ELISA kits, as the normal range of CA15.3 was < 30 U/mL. The hormones, specifically Estradiol (E2) and Progesterone (P4), were measured using ELISA kits from BioCompare. The hormonal profiling such as serum Estradiol (E2) kits the normal range of (E2) was (12.5 - 50) pg/mL and Progesterone (P4) levels obtained from

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ELISA kits for human samples the normal range of (P4) was (1-1.5) ng/mL; renal function parameters of Urea and Creatinine were determined using spectrophotometric techniques using Bio-system kits the normal range of Urea was (15-45) mg/dL and normal range of Creatinine was (0.7-1.3) mg/dL, according to the manufacturers' instructions.

Statistical Analysis

All analyses were performed using SPSS version 26 and Microsoft Excel 2016. A one-way ANOVA indicated statistically significant differences among the study groups. The data were analyzed using the collected data. Descriptive statistics (Mean ± SD) were estimated. Comparisons between groups were performed with the Independent T-test, and the ROC Curve was utilized. Pearson's correlation was employed to assess the association of renal markers and hormonal levels. A (P-value) < 0.05 was considered statistically significant.

Results:

The study sample was stratified into three groups to determine the influence of renal function on hormonal levels in breast cancer patients. The comparisons are between patients with normal renal function (n=40), those with impaired renal function (n=40), and the control group (n=80) with normal physiological levels; the distribution is shown in Table 1.

Tables 2 & 3 illustrated that the biochemical profiles of participants revealed highly statistically significant differences between breast cancer patients with normal renal function and those with renal dysfunction, compared with healthy controls, for serum CA15-3, progesterone, estradiol (E2), urea, and creatinine. The statistical analysis using one-way ANOVA across the study groups (Group A, Group B, and Group C) revealed distinct patterns of significance across the measured parameters:

Hormonal Profile (Estradiol & Progesterone):

Estradiol (E2) levels decreased significantly in Group A compared to Group B ($P < 0.05$), and both groups showed a highly significant reduction ($P < 0.001$) compared to the control (Group C). Similarly, Progesterone (P4) levels showed no significant difference between Groups A and B ($P = 0.94$), whereas both remained highly significantly different from the control group ($P < 0.001$).

Tumor Marker (CA 15.3):

Statistical analysis of CA 15.3 indicated no significant difference between Group A and Group B ($P = 0.1296$). However, consistent with the hormonal data, a highly significant decrease ($P < 0.001$) was observed when comparing the cancer groups (A and B) against the healthy control (Group C).

Renal Function Markers (Urea & Creatinine):

Serum creatinine levels demonstrated the most consistent and highly significant variation ($P < 0.001$) across all study groups, showing a significant increase between A and B, and a decrease when comparing A and B against Group C. In contrast, Urea showed no significant difference between groups A and C; interestingly, the comparison between A and B was highly significant, while that between B and C was significant.

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Table (1). Distribution of the Study Group

Group	Description	Number of sampling (N)
A	Breast cancer patients with normal renal function	40
B	Breast cancer patients with impaired renal function	40
C	Healthy individuals (Control group)	80
		Total = 160

Table (2). Mean and SD of studied parameters between Groups.

Parameter	Group A (Cancer/Normal Renal)	Group B (Cancer/Impaired Renal)	Group C (Control/Healthy)	*P*-value
Estradiol (E2) (pg/mL)	10.77±5.98	8.87±3.85	44.37± 8.89	<0.001**
Progesterone (P4) (ng/mL)	0.31±0.45	0.25±0.51	1.05 ±0.26	<0.001**
Urea(mg/dL)	26.2±5.88	78±9.22	26.09±6.37	<0.001**
Creatinine (mg/dL)	0.83±0.12	2.28 ±0.53	0.62±0.16	<0.001**
CA15.3 (U/mL)	40.67± 20.71	47.62±19.88	11.10± 3.65	<0.001**

*** Highly significant difference at p-value ≤ 0.001 level*
Note: p > 0.05 indicates no statistically significant difference between the groups.

Table (3) Statistical Comparison between Renal function and Hormonal levels among the study groups.

Parameter	Group Comparison	ANOVA	*P*-value
Estradiol (E2) (pg/mL)	A vs. B	-5.811	<0.05
	A vs. C	23.702	<0.001**
	B vs. C	25.258	<0.001**
Progesterone (P4) (ng/mL)	A vs. B	-2.451	0.94
	A vs. C	13.573	<0.001**
	B vs. C	14.569	<0.001**
CA 15.3 (U/mL)	A vs. B	1.532	0.1296
	A vs. C	-12.440	<0.001**
	B vs. C	-15.966	<0.001**
Urea	A vs. B	29.966	<0.001**
	A vs. C	-0.0665	0.9471
	B vs. C	-36.058	<0.001**
Creatinine (mg/dL)	A vs. B	16.882	<0.001**
	A vs. C	-4.195	<0.001**
	B vs. C	-24.227	<0.001**

*** Highly significant difference at p-value ≤ 0.001 level.*
***Note:** p > 0.05 indicates no statistically significant differences between the groups.*

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The diagnostic potential of the studied biomarkers was further corroborated by the ROC curves and the detailed parameters shown in Table 4. E2 and P4 exhibited a remarkably strong diagnostic capacity with an Area Under the Curve (AUC) of 0.99 ($P < 0.001$) and AUC = 0.910 ($P < 0.001$), respectively. Diagnostic performance of the studied markers is shown in Figure 2. Both CA15.3 and E2 had a perfect Area Under the Curve, and their lines overlapped at the top-left corner of the plot, indicating high sensitivity and specificity at their respective cut-off points. ROC curve for serum Urea demonstrating a non-significant diagnostic discriminatory power, AUC = 0.757 ($P < 0.001$). Creatinine AUC = 0.868 ($P < 0.001$). By ROC curve (Table 4, Fig. 4). By comparison, Urea showed a lower diagnostic utility compared to other markers, with an AUC of 0.757 and a significant P-value (< 0.001), indicating a moderate ability to distinguish between the groups. However, despite Urea's moderate sensitivity (52.50%), the correlation analysis in Figure 3 indicates a more physiological level of association.

Table (4) ROC Curve Parameters for Diagnostic Performance

Biomarker	AUC (Area Under Curve)	Cut-off Point	Sensitivity (%)	Specificity (%)	Std. Error	*P*-value
CA15.3	0.999	>18	100%	97.50%	0.0294	< 0.001**
Estradiol (E2)	0.99	≤15	100%	100.00%	0	< 0.001**
Progesterone (P4)	0.910	≤0.73	100%	86.25%	0.0293	< 0.001**
Creatinine	0.868	>0.9	63.75%	96.25%	0.0270	< 0.001**
Urea	0.757	>40	52.50%	97.50%	0.0393	< 0.001**

***Highly significant difference at p-value ≤ 0.001 level*

Note: p > 0.05 indicates that the difference between the groups is not statistically significant.

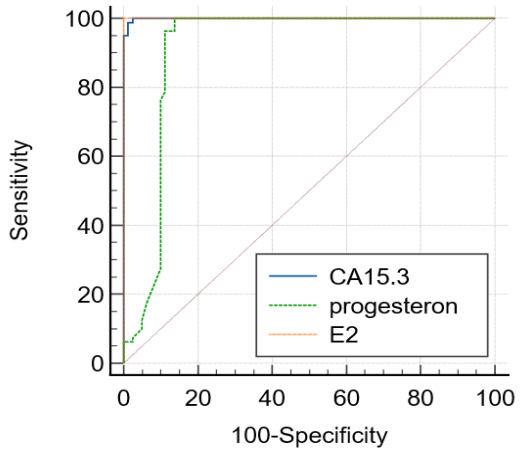

Figure 2: *Diagnostic Efficiency and ROC Curve Analysis of serum CA15.3, Progesterone, and E2*

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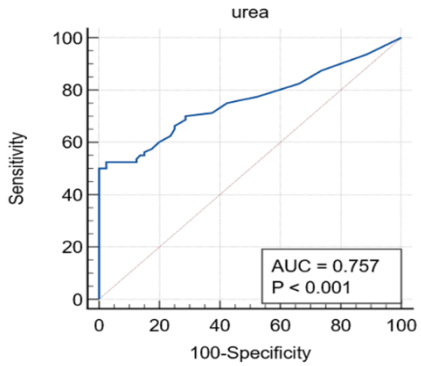

Figure 3: *Graphical representation of the ROC curve for serum Urea*

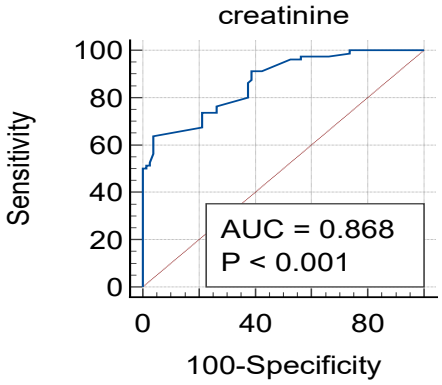

Figure 4: *Graphical Representation of the ROC curve for serum Creatinine*

Table 5: Pearson's Correlation Coefficients (r) of Renal Markers in Relation to Hormonal Levels.

Variables	**Correlation Coefficient (r)**	**(*p*-value)**
Estradiol (E2) vs. Creatinine	-0.5728	<0.001**
Estradiol (E2) vs. Urea	-0.5728	<0.001**
Progesterone (P4) vs. Creatinine	-0.5212	<0.001**
Progesterone (P4) vs. Urea	-0.4831	<0.001**
CA15.3 vs. Creatinine	0.5442	<0.001**
CA15.3 vs. Urea	0.5176	<0.001**
CA15.3 vs. Estradiol (E2)	-0.6945	<0.001**
CA15.3 vs. Progesterone (P4)	-0.6400	<0.001**

** *Highly significant difference at p-value ≤ 0.001 level.*
Note: If p > 0.05, then there was no statistically significant difference between the groups.

Pearson's correlation analysis indicated that Urea showed a highly significant positive correlation with the tumor marker CA15.3 (r = 0.5176, p<0.001), and CA15.3 showed a

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significant positive correlation with Creatinine ($r = 0.5442$, $p < 0.001$). In addition, a strong negative correlation was found between Estradiol (E2) and both Urea and Creatinine ($r = -0.5728$, $r = -0.5728$, $p < 0.001$). Moreover, strong negative correlations were found between Progesterone (P4) and both Urea and Creatinine ($r = -0.4831$, $r = -0.5212$, $p < 0.001$).

Discussion

The results of this study have been particularly noteworthy, with significantly lower serum Estradiol (E2) levels in Groups A and B compared with the control group ($P < 0.001$). Nevertheless, the findings indicate that decreased serum estradiol levels are frequently observed in patients with breast cancer due to treatment (e.g., aromatase inhibitors, chemotherapy), signifying a measure of treatment success rather than a fundamental trait of the illness. Research indicates that increased E2 increases risk, while low E2 serves as a treatment goal rather than a primary differentiator between breast cancer patients and healthy subjects (16).

Furthermore, the present study showed a statistical significance difference in Estradiol (E2) level ($P < 0.001$) between the BC patients in Group A and Group B and the healthy controls Group C. Additionally, the findings indicated a highly significant difference in Progesterone (P4) levels between Group A vs. Group C ($P < 0.001$) and Group B vs. Group C ($P < 0.001$) . Regarding the tumor marker CA 15.3, the study observed a highly significant difference ($P < 0.001$) in group A vs group C. The association between hormonal imbalance and elevated tumor marker levels highlights the difference in the biological profile of the control group (Group C). In contrast, the similarities observed between groups A and B indicate comparable disease characteristics (17-19).

Furthermore, Serum creatinine levels showed a highly statistically significant difference ($P < 0.001$) between group A and group B compared with the control group. The marked increase in creatinine levels in group B with breast cancer patients is attributed to the cumulative effect of nephrotoxicity resulting from chemotherapy protocols and the oxidative stress associated with breast cancer. This leads to impaired glomerular filtration efficiency and the accumulation of metabolic waste products in the blood, which is directly proportional to the severity of renal failure compared to healthy individuals. This is consistent with the study (20). Our study results indicate that the severe increase in urea levels in group B in renal filtration efficiency resulting from chemotherapy-related nephrotoxicity and the deterioration of glomerular function with increased systemic protein breakdown caused by cancer, both of which lead to a significant accumulation of nitrogenous wastes in the blood, compared to the control and healthy groups. This is consistent with the study (20). Additionally, our study results demonstrated that Estradiol (E2), Progesterone (P4), and the tumor marker CA15.3 exhibited the highest discriminatory accuracy, as indicated by the AUC. This reflects their efficiency in accurately separating patient and healthy groups at optimal cut-off points. Furthermore, creatinine and urea showed high diagnostic accuracy (AUCs of 0.868 and 0.757, respectively) with very high specificity exceeding 96%. This underscores their role as warning indicators for identifying renal impairment resulting from chemotherapy-induced nephrotoxicity in breast cancer patients. Previous research also supports their use as

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accurate clinical screening indicators to ensure patient safety during treatment (21,22,23). This association highlights demonstrated a strong and statistically significant inverse relationship between estradiol (E2) and Progesterone (P4) levels and both creatinine ($r = -0.57$, $P < 0.001$, $r=-0.52$, $P < 0.001$) respectively, and urea ($r = -0.57$, $P < 0.001$, $r =--0.48$, $P < 0.001$) respectively, this indicates a decrease in renal filtration efficiency, which is inversely proportional to the sharp decline in hormone levels in breast cancer patients. This decline is physiologically caused by the effects of chemotherapy and impaired metabolic status, leading to nephrotoxicity. The sharp decrease in estradiol (E2) and Progesterone (P4) coincides with impaired renal excretion, causing these two variables to move in opposite directions. Our findings are consistent with previous research (24). Our results for the tumor marker CA 15-3 and renal function indicators (creatinine and urea) showed a strong positive correlation ($r = 0.54$, $P < 0.001$) and ($r = 0.51$, $P < 0.001$), respectively, and a strong clinical correlation between elevated tumor levels and deteriorating renal function. Clinically, this correlation is attributed to the fact that increased tumor size necessitates more intensive chemotherapy protocols, which significantly impact the renal tubules (nephrotoxicity). The resulting renal impairment reduces the body's elimination of metabolites and tumor markers, leading to toxin accumulation in the bloodstream and, consequently, nephropathy. This relationship underscores the importance of monitoring renal function as a key component of the protocol for assessing tumor activity and ensuring patient safety during treatment. Previous research supports our findings (25). Furthermore, this study's notable negative associations between CA15-3 and progesterone (P4) and estradiol(E2) ($r = -0.64$, $P < 0.001$) and ($r = -0.69$, $P < 0.001$) respectively, highlight the therapy-induced state of hormonal suppression and the association with increased tumor marker levels. These results agree with previous research (26,27).

Conclusion

Diminished kidney function creates a complex environment that promotes tumors and significantly influences the pathophysiology of BC. The relationship is driven by a combination of hormonal imbalance, chronic inflammation, and altered toxin metabolism, which together promote cancer growth and advancement.

Ethical statement

Patients provided verbal consent, and information was collected via a questionnaire. The ethical approval for this study was obtained from the Ethics Committee at the College of Medicine, Al-Iraqia University (FM.SA26-8/2/2026).

Conflict of interest: The author declares no conflicts of interest.

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