A Study on the Role of LPA and ATX in Breast Cancer in Iraq

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Abstract- Breast cancer is the most common malignancy among women and a leading cause of cancer-related mortality. Early detection is crucial for improving treatment outcomes. This study investigates the roles of lysophosphatidic acid (LPA) and autotaxin (ATX) in the early diagnosis of breast cancer among Iraqi women. A case-control study was conducted involving 75 women diagnosed with breast cancer and 75 healthy controls. Blood samples were collected, and biochemical parameters, including LPA and ATX levels, were measured using the ELISA technique. Statistical analyses were performed with SPSS version 24, and receiver operating characteristic (ROC) analysis was used to evaluate diagnostic capabilities. The majority of breast cancer patients were aged 50-59 years (33.3%). Histologically, invasive ductal carcinoma was the most prevalent subtype (82.6%). Biochemical analysis revealed significant differences in alanine aminotransferase, total serum bilirubin, and alkaline phosphatase levels between patients and controls. LPA levels were significantly elevated in the patient group (868.48±142.11 pg/ml) compared to controls (212.01±54.94 pg/ml), while ATX levels were also higher (2252.20±399.46 pg/ml vs. 951.40±209.21 pg/ml). ROC analysis indicated that both LPA and ATX exhibited high diagnostic sensitivity (98%) and specificity (100%). In Iraqi women, elevated serum levels of LPA and ATX may serve as potential diagnostic biomarkers for breast cancer, highlighting their role in disease progression. Further studies are warranted to explore their clinical applications in breast cancer diagnosis and management.

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Introduction

Breast cancer is the most prevalent cancer among women and the leading cause of death in this demographic (1-3). It originates from the abnormal growth of specific breast cells that divide more rapidly than normal cells, resulting in the formation of a malignant mass (4-6). These malignant cells possess the ability to metastasize within the lymph nodes and breast tissue and potentially disseminate to other regions of the body (3). Early diagnosis, innovative treatment strategies, and a better understanding of the disease have significantly improved survival rates and gradually decreased breast cancer mortality (7). Early detection is crucial because it prevents the spread of cancer to other parts of the body, which improves treatment outcomes (5).

There is increasing evidence that lysophosphatidic acid (LPA) plays a physiological role in regulating tumor growth, angiogenesis, and metastasis (8). LPA is a bioactive phospholipid that binds to at least six different receptors, known as LPAR1-6. Each receptor is associated with a distinct G-protein, which enables cells to perform various functions such as movement, proliferation, and differentiation (9). Autotaxin (ATX) is a glycoprotein encoded by the ENPP2 gene and is a member of the Ectonucleotide Pyrophosphatase Phosphodiesterase (ENPP) family (10). Its expression is dependent on growth factors, cytokines, and hormones (11).

ATX was first discovered in melanoma cells (12). Subsequent research showed that ATX is not restricted

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to melanoma cells; it is also produced by platelets, endothelial cells, fibroblasts, and adipocytes. This indicates that adipocytes are a significant source of ATX in tumors (13). Breast cancer is a human cancer that has adipocyte-rich stroma (14). ATX was first thought to work as a pyrophosphatase (8), but later research showed that it could also break down lysophosphatidic choline (LPC) into lysophosphatidic acid (LPA) (15).

Both ex vivo and in vivo research indicates that elevated ATX-LPA signaling activity may play a significant role in cancer development and progression (16). Importantly, ATX and LPA have been recognized as potential diagnostic biomarkers and drug targets for cancer and chronic inflammatory diseases (17). This study aims to investigate the roles of LPA and ATX in newly diagnosed breast cancer among Iraqi women, emphasizing their potential contributions to early diagnosis and disease progression.

Materials and Methods

Study design

This observational case-control study involved 75 Iraqi women aged 23 to 72 who were newly diagnosed with breast cancer. Samples were collected from Al-Amal National Hospital for Oncology Treatment and Al-Alwaiya Maternity Teaching Hospital, specifically from the Women's Health Department Unit of Early Detection of Breast Cancer in Baghdad, Iraq, between February 2024 and June 2024. Blood samples were obtained following several diagnostic procedures, including clinical examinations, ultrasounds, mammograms, and various laboratory tests. A histological examination (biopsy) was performed to confirm the breast cancer diagnosis.

Additionally, a control group comprising 75 apparently healthy women aged 22 to 70 was included in the study. These women had no tumors, fibrosis, masses, or inflammation in the breast, confirmed through clinical examinations, ultrasounds, and mammograms. Participants in the study group were excluded if they were pregnant, had metastatic breast cancer, or had received radiation, chemotherapy, immunotherapy, or hormonal therapy. Women who had undergone lumpectomy or mastectomy were also excluded, as were those with chronic illnesses such as diabetes, hypertension, myocardial diseases, renal diseases, pancreatic diseases, pulmonary diseases, and breast fibroadenoma.

Sampling

Five milliliters of venous blood were collected and placed in a dry, clean gel tube without an anticoagulant. To ensure accurate identification, each tube was labeled with a unique code corresponding to the participant. The blood was allowed to clot for 10-15 minutes at room temperature before being centrifuged at 2000-3000 RPM for 10 minutes to separate the serum. The serum was then distributed into four sterile, tightly closed Eppendorf tubes and stored at -80° C in a deep freezer until analysis. Blood biochemical parameters, including aspartate aminotransferase, alanine aminotransferase, total serum bilirubin, and alkaline phosphatase, were measured using a Roche Cobas C311 Chemistry Analyzer. The levels of LPA in the serum were assessed using ELISA (Cloud-Clone Corp., USA), while ATX levels were measured by ELK Biotechnology (USA).

Statistical analysis

Statistical analysis was conducted using SPSS version 24. Digital frequencies and percentages were calculated, followed by an independent sample t-test to assess the significance of LPA, ATX, and biochemical tests (ALT, AST, TSB, and ALP). A receiver operating characteristic (ROC) analysis was performed to evaluate the sensitivity and specificity of serum ATX and LPA in distinguishing between individuals with breast cancer and healthy controls. Additionally, Pearson's correlation analyses were employed to examine the correlation between LPA and ATX parameters. A *P* of less than .05 was considered statistically significant.

Results

Demographic characteristics of study groups

The demographic characteristics of the patient group and the healthy control group are presented in Table 1. The most affected age group among patients was 50-59 years, comprising 25 individuals (33.3%). The next most affected group was 60-70 years, with 22 individuals (29.3%). Additionally, 18 patients (24.0%) were aged 40-49 years, and 10 patients (13.3%) were in the <30-39 years age group. This indicates that over 60% of the patients were over the age of 50. Of the 60 women diagnosed with breast cancer, 45 (60.0%) did not have a family history of the disease, while 30 (40.0%) did have a family history. Most women in the study had one to two children (53.3%), while slightly fewer had three to four children (28.0%), and 18.7% had five to seven children. Regarding breastfeeding, 40 (53.3%) of the breast cancer patients had a positive breastfeeding history, whereas 35 (46.7%) had a negative

breastfeeding history.

Table 1. Demographic characteristics of study group

			Group Study	
			Control (n=75)	Patient (n=75)
Age groups	(<30-39)	No.	15	10
		%	20.0%	13.3%
	(40-49)	No.	13	18
		%	17.3%	24.0%
	(50-59)	No.	30	25
		%	40.0%	33.3%
	(60-≥70)	No.	17	22
		%	22.6%	29.3%
Family history	no	No.	75	45
		%	100.0%	60.0%
	yes	No.	0	30
		%	0.0%	40.0%
Number of children	(1-2)	No.	30	40
		%	40.0%	53.3%
	(3-4)	No.	34	21
		%	45.3%	28.0%
	(5-≥7)	No.	11	14
		%	14.7%	18.7%
Breast feeding	no	No.	27	35
		%	36.0%	46.7%
	yes	No.	48	40
		%	64.0%	53.3%

Histologic types of breast cancer

Table 2 presents the histologic types of breast cancer among patients. The predominant diagnosis was invasive ductal carcinoma, which occurred in 62 cases (82.6%). This was followed by invasive lobular carcinoma, with 8 cases (10.7%). Invasive mucinous carcinoma was identified in 2 cases (2.7%), while mixed types of breast cancer were also found in 2 cases (2.7%). Additionally, ductal carcinoma in situ was reported in 1 case (1.3%).

Table 2. displays the histologic types of breast cancer

Histologic types of breast cancer	No.	%
Invasive ductal carcinoma	62	82.6
Invasive lobular carcinoma	8	10.7
invasive mucinous carcinoma	2	2.7
Mixed type of breast cancer (Ductal+ Lobular Carcinoma)	2	2.7
Ductal carcinoma in situ	1	1.3
Total	75	100.0

Comparison of biochemical tests between patients and control

Table 3 indicates a significant reduction in ALT levels in the patient group (17.84±7.33) compared to the control group (21.43±3.58), with a *P* of less than 0.01. The study also reveals a significant increase in TSB levels in the patient group (0.52±0.30) relative to the control group (0.29±0.15), with a *P* below 0.01. Additionally, ALP levels are significantly higher in the patient group (66.82±21.36) compared to the control group (56.87±10.70), with a *P* under 0.01. In contrast, AST levels do not show a significant difference between the patient group (18.52±4.93) and the control group (19.70±3.47), as indicated by a *P* greater than 0.05.

Comparison of LPA and ATX between patient and control groups.

Table 4 demonstrates that LPA levels were significantly higher in the patient group (868.48±142.11) than in the control group (212.01±54.94), with a *P* of 0.000. Similarly, ATX levels were markedly elevated in the patient group (2252.20±399.46) compared to the control group (951.40±209.21), also yielding a *P* of 0.000.

Pearson correlations between LPA and ATX in the

patient group

Table 5 displays the Pearson correlations between the markers LPA and ATX in the patient group. The analysis revealed no significant correlation between LPA and ATX.

ROC analysis for the studied parameters among the breast cancer and healthy control groups

According to Table 6 and Figures 1 and 2, the ROC analysis showed that both LPA and ATX had an area under the curve (AUC) of approximately 0.99. These biomarkers demonstrated high sensitivity, typically exceeding 97%, and had significant *P* of less than 0.001, indicating strong statistical robustness.

Table 3. Comparison of biochemical tests between patient and control groups

	Group Study	Mean± Std.	t-test	*P*
ALT(<35)U/L	Control	21.43±3.58	3.412	*P*=.001
	Patient	17.84±7.33		*P*<0.01(HS)
AST(<35)U/L	Control	19.70±3.47	1.514	*P*=.133
	Patient	18.52±4.93		P>0.05(NS)
Total Bilirubin(<0.9)U/L	Control	0.29±0.15	5.246	*P*=.000
	Patient	0.52±0.30		*P*<0.01(HS)
ALP(35-104)U/L	Control	56.87±10.70	3.226	*P*=.002
	Patient	66.82± 21.36		*P*<0.01(HS)

Table 4. Comparison of LPA and ATX between patient and control groups.

	Group Study	Mean± Std.	t-test	*P*
LPA	Control	212.01±54.94	33.376	*P*=.000
	Patient	868.48±142.11		*P*<0.01(HS)
ATX	Control	951.40±209.21	22.345	*P*=.000
	Patient	2252.20±399.46		*P*<0.01(HS)

Table 5. Pearson correlations between LPA and ATX in the patient group

		LPA	ATX
LPA	**Correlation**	**1**	**-0.15**
	Sig. (*P*)		**0.19NS**
ATX	**Correlation**	**-0.15**	**1**
	Sig. (*P*)	**0.19NS**	

Table 6. ROC analysis for studied parameters among breast cancer and healthy control groups

Markers	AUC	*P*	Cut-off Point	Sensitivity	Specificity
LPA	.98	.000	465	98%	100%
ATX	.99	.000	1499	98%	100%

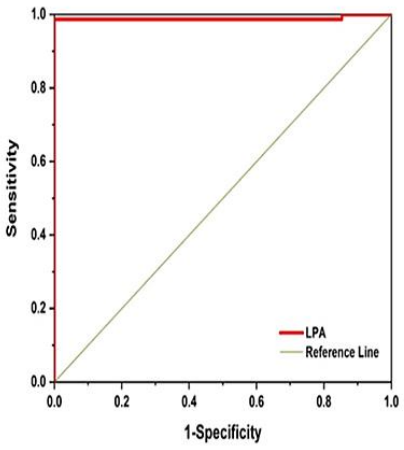

Figure 1. ROC curve for LPA activity

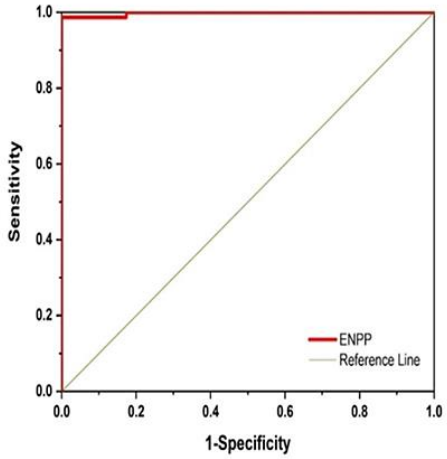

Figure 2. ROC curve for ATX activity

Discussion

Breast cancer is the most common cancer among women and the leading cause of cancer-related deaths (18). Several factors increase the risk of developing breast cancer. These include sex, age, reproductive factors like the number of children a woman has and whether she has breastfed, as well as genetic factors and family history (19). In the current study, the age distribution of breast cancer patients showed that the largest group was women aged 50-59 years, comprising 33.3% of the sample. In contrast, the smallest group included those aged 30-39 years, making up 15.0%. These findings are consistent with another study that identified the largest group as women aged 51-65 years (35.7%) and the smallest group as those aged 40 years or younger (16.5%) (20). The incidence of breast cancer generally increases with age, affecting older women (21).

Breast cancer in older women may result from age-related changes in hormonal levels, inflammatory cytokines, and immune dysfunction, all of which can contribute to a tumor-permissive environment in breast tissue (22). A family history of breast cancer was also examined in our study. The results revealed that 60.0% of the women did not have a family history of the disease, whereas 40.0% did. These findings align with previous research, which found that 59.6% of women lacked a family history, while 40.4% had one (23). Similarly, another study indicated that 62.5% of women didn't have a family history, with 37.5% having family history (24). Exposure to certain chemicals and radiation, along with lifestyle factors such as obesity, has been associated with a higher risk of breast cancer, regardless of family history (25).

In our study, most women (53.3%) reported having one to two children. This finding aligns with another study, which found that the majority of women had two children (32.7%), followed by one child (21.3%), three children (13.3%), four children (8.0%), and more than four children (4.9%) (26). Among parous women, having fewer children is associated with an increased risk of breast cancer. This may be related to a smaller proportion of epithelial tissue and a greater proportion of stromal tissue, highlighting the importance of epithelial-stromal interactions (27).

Among the patient group, 40 women (53.3%) reported that they had breastfed, while 35 women (46.7%) reported that they had not. This is consistent with findings from a study (28), which indicated that (57.6%) of women had breastfed, whereas (42.4%) had not. In this study, invasive ductal carcinoma was the most prevalent histological subtype, representing 82.6% of all cases. Another study (29) also found that invasive ductal carcinoma was the most common type of breast cancer (91.5% of cases). This is due to the fact that it originates in ductal epithelial cells, tends to form detectable masses, and grows differently compared to other types of breast cancer, such as invasive lobular carcinoma (30).

In the current study, the patient group exhibited significantly lower ALT levels than the control group, despite the mean ALT remaining within the normal range. Similarly, It has been reported (31) that patients exhibited a significant decrease in ALT levels compared to controls. This suggests that low ALT levels may

indicate minimal hepatic involvement in early-stage cancer patients. In contrast, total bilirubin levels were significantly elevated in the patient group compared to the control group, which aligns with findings from another study (32) that also noted a significant difference in bilirubin levels between the two groups. While bilirubin has traditionally been viewed as a waste product, recent research (33) recognizes it as an important antioxidant that helps mitigate oxidative stress in various diseases, including cancer.

ALP levels were significantly higher in the patient group than in the control group, although the mean ALP stayed within the normal range. Previous studies have indicated that ALP activity tends to increase with age, especially in postmenopausal patients and those with metastatic breast cancer (34). This increase may be due to bone damage in postmenopausal women, which leads to elevated ALP levels (35). The ATX-LPA signaling axis activates various G protein-coupled receptors (GPCRs) and plays a role in numerous biological processes, including breast cancer growth (36). Our study found that LPA levels were significantly higher in the patient group than in the controls. This aligns with findings from another study, which reported similar elevations in LPA levels among breast cancer patients (37). Our results also indicated that ATX levels were significantly higher in the patient group. This finding aligns with a previous study (36) that reported elevated ATX levels in the serum of breast cancer patients. In our study, ATX displayed an AUC of 0.99, with a sensitivity of 98% and a specificity of 100%, highlighting its robust diagnostic capability.

It has been reported (36), that ATX has an AUC of 0.798, a sensitivity of 74%, and a specificity of 80%. While our study demonstrated a higher sensitivity compared to previous research, both studies highlight the diagnostic potential of ATX. The differences in sensitivity may arise from variations in study design, sample characteristics, or measurement techniques. Additionally, there are no studies on breast cancer that include ROC curve analyses for LPA.

In Iraqi women, elevated serum levels of LPA and ATX may serve as potential diagnostic biomarkers for breast cancer, highlighting their importance in disease progression. Further research is needed to explore their clinical applications in the diagnosis and treatment of breast cancer.

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