International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2024; 7(3): 258-266
Received: 23-06-2024
Accepted: 30-07-2024

Noor Kareem Abes
Babylon Health Directorate, Babylon, Iraq

Hadeel Abdulelah Karbel
Hammurabi Medical College, University of Babylon, Babylon, Iraq

Corresponding Author:
Noor Kareem Abes
Babylon Health Directorate, Babylon, Iraq

Prognostic values of cyclooxygenase-2 in invasive breast cancer

Noor Kareem Abes and Hadeel Abdulelah Karbel

DOI: https://doi.org/10.33545/pathol.2024.v7.i3d.610

Abstract

Background: Breast cancer remains a significant global health issue, notably affecting women, with high prevalence and mortality rates. Cyclooxygenase-2 (COX-2) is a key molecular contributor to breast cancer development, with increased COX-2 expression correlating with poor outcomes and treatment resistance, highlighting its prognostic value.

Aim of the study: To evaluate the immunohistochemical (IHC) expression of COX-2 in breast cancer and correlate its expression with various prognostic factors.

Materials and Methods: This cross-sectional study was conducted at the "Babylon Training Center for Pathology" from January to December 2023. A total of 50 invasive breast cancer cases were analyzed. The mean patient age was 53.56 years. IHC techniques were used to assess COX-2 expression.

Results: COX-2 expression was positive in 80% of the patients. Histological analysis classified 90% of cases as invasive ductal carcinoma (IDC NST), with 68% being luminal A and B subtypes. No significant associations were found between COX-2 expression and histological diagnosis, *In-situ* component presence, or histological grade. However, significant associations were observed between COX-2 expression and hormone receptor status, with 62% positive for estrogen receptors, 58% for progesterone receptors, and 44% for HER2 receptors. Notably, COX-2 expression intensity significantly correlated with progesterone receptor expression ($p = 0.005$). Molecular classification analysis revealed no significant association with COX-2 expression.

Conclusion: There is a statistically significant inverse relationship between COX-2 expression and hormone receptor status, particularly with estrogen and progesterone receptors. This suggests COX-2's potential role as a predictive biomarker for the aggressive nature of breast cancer, underscoring its prognostic implications.

Keywords: Prognostic, values, cyclooxygenase-2, invasive, breast, cancer

Introduction

Breast cancer is a significant global health issue, particularly affecting women, as evidenced by recent statistics from the World Health Organization and the Iraqi cancer registry. It is the most common cancer among women worldwide, with over two million new cases diagnosed annually [1, 2]. Epidemiological data reveal a concerning trend, with breast cancer affecting more than one in ten women globally, leading to substantial morbidity and mortality. Incidence rates are particularly rising in older age groups [1]. Understanding the risk factors associated with breast cancer is essential for prevention and targeted interventions. Both non-modifiable factors such as age and gender and modifiable factors such as diet, physical activity, and hormonal influences significantly contribute to disease development [3]. The histological classification of breast cancer identifies its various subtypes, including both in situ and invasive cancers. This classification aids in diagnosis, treatment decisions, and prognostic assessments [4]. Additionally, immunohistochemistry techniques provide valuable insights into tumor subtypes, hormone receptor status, and HER-2 expression, which are crucial for personalized treatment approaches [5]. Cyclooxygenase-2 (COX-2) is a key molecular player in breast cancer pathogenesis, involved in various tumorigenesis aspects, including apoptosis resistance, angiogenesis, metastasis, and inflammation. Elevated COX-2 expression in breast cancer cells is linked to poorer outcomes and resistance to conventional therapies, highlighting its potential as a prognostic marker [6, 7]. Aim of the study is to evaluate the IHC expression of COX-2 in breast cancer and to correlate its expression with different prognostic factors.

Method

This cross-sectional study was conducted at the Babylon Training Center for Pathology from January 2023 to December 2023. The study included 50 cases of invasive breast cancer.

Patient selection criteria

Inclusion criteria

- Women of any age with confirmed invasive breast cancer diagnosed through microscopic examination using standard hematoxylin and eosin staining.

Exclusion criteria

- Breast tumors diagnosed as benign or mesenchymal.
- *In-situ* breast tumors only.
- Females with invasive breast cancer who received radiation, chemotherapy, or COX inhibitors before assessment.
- Male breast cancer cases.
- Cases with missing data.

Data Collection

Data were collected from Teba Private Hospital in Babylon from January 2023 to July 2023. The paraffin blocks for the 50 cases were retrieved from the laboratory archives. Clinicopathological data were collected, and estrogen receptor (ER), progesterone receptor (PR), and HER2 status were re-evaluated by an expert pathologist. Each tissue block was sectioned at 5 micrometers for hematoxylin and eosin (H&E) staining. Primary antibody COX-2 (Rabbit monoclonal antibody, clone: EP293) from PathnSitu Biotechnologies was used. The Poly Excel HRP/DAB detection system was employed for immunostaining.

1. **Tissue Preparation:** Formalin-fixed, paraffin-embedded tissue sections were affixed to positive charged slides.
2. **Deparaffinization and Rehydration:** Sections were incubated at 60 °C for 2 hours, followed by xylene and ethanol series for rehydration.
3. **Epitope Retrieval:** Tris-EDTA buffer was used under steam pressure at 95 °C for 20 minutes, then cooled at room temperature and washed in distilled water.
4. **Endogenous Peroxidase Blockage:** Polydetector Peroxidase Blocker was applied for 5 minutes.
5. **Primary Antibody Incubation:** Sections were incubated with primary antibody for 60 minutes at room temperature.
6. **Chromogen Application:** DAB substrate-chromogen solution was applied for 10 minutes.
7. **Counterstaining:** Hematoxylin counterstaining was performed followed by dehydration and mounting.

Quality Controls

Positive and negative control sections were included in each staining set. Colon cancer tissues served as positive controls, and sections without primary antibody were negative controls.

Scoring system

COX-2 expression was scored based on staining intensity and percentage of positive cells. The Immuno-Histochemical Score (IHS) ranged from 0 to 12:

- 0-3: Negative or faint staining.
- 4-8: Moderate/intermediate staining.
- 9-12: Strong/high staining.

ER and PR statuses were assessed following ASCO/CAP guidelines and scored based on intensity and proportion of positive cells. Final receptor scores categorized as:

- 0, 1, 2: Negative.
- 3-4: Mild positive.
- 5-6: Moderate positive.
- 7-8: Strong positive [8, 9].

Statistical Analysis

Data were analyzed using SPSS version 26. Frequencies, percentages, means, standard deviations, and ranges were used to present the data. ANOVA was used to test differences among means, and Pearson Chi-square or Fisher Exact test was used for qualitative data. Statistical significance was set at $p \leq 0.05$.

Results

The study assessed the intensity of estrogen and progesterone receptor expressions, histological grading of tumors, and COX-2 status in breast cancer patients. For estrogen receptors, 22% of patients had mild expression, 20% had moderate expression, and another 20% had strong expression. Progesterone receptor testing showed 30% with mild expression, 16% with moderate expression, and 12% with strong expression. Histological grading revealed that the majority of patients (72%) had grade II breast cancer, 20% had grade I tumors, and 8% had grade III tumors. COX-2 status indicated that 80% of patients had COX-2 expression, while 20% lacked it. The intensity of COX-2 expression showed 20% had negative expression, 66% had moderately positive expression, and 14% had strong positive expression.

Table 1: Distribution of breast cancer cases according to different clinicopathologic parameters (age, histopathological diagnosis, *In-situ* component, tumor grade, hormonal profile, HER-2 status and COX-2 expression)

Clinicopathological parameter		Frequency	Percent
Age	Mean ± SD		53.56±13.1 (31-82)
Age group	20-39 years old	9	18.0%
	40-59 years old	24	48.0%
	60-79 years old	14	28.0%
	>80 years old	3	6.0%
Histological diagnosis	IDC NST	45	90.0%
	ILC	5	10.0%
In-situ component status	Present	6	12.0%
	Absent	44	88.0%
ER expression	Negative	19	38.0
	Mild	11	22.0
	Moderate	10	20.0

	Strong	10	20.0
PR expression	Negative	21	42.0
	Mild	15	30.0
	Moderate	8	16.0
	Strong	6	12.0
HER2 receptor status	Positive	22	44.0%
	Negative	28	56.0%
Histological grade	I	10	20.0%
	II	36	72.0%
	III	4	8.0%
Molecular classification	Luminal A and B	34	68.0%
	HER2 enriched	10	20.0%
	TNBC	6	12.0%
COX-2 expression	Strongly positive	7	14.0%
	Moderately positive	33	66.0%
	Negative	10	20.0%

For the association between histological types (ductal and lobular) and COX-2 expression, there was no statistically significant difference with p-value of 0.99 (Table 2). Likewise, the association between the statuses of *In-situ* component presence with COX-2 expression showed no statistically significant difference with p-value of 0.192. The histological grade when studied in association with COX-2 expression showed no statistically significant difference with p-value of 0.671. For the association of hormone receptors status with COX-2 expression. There was a statistically significant association for estrogen receptor expression and progesterone receptor expression with COX-2 receptor status with p-value <0.05. Meanwhile, there was no statistically significant association of HER2 receptor status with p-value of 0.154. For the association of molecular classification according to IHC with COX-2 expression. There was no statistically significant association between the two with p-value of 0.215. As in table 2.

Table 2: Molecular classification of breast cancer association with COX-2 expression

			COX-2 status		**Total**	**P-value**
			Positive	**Negative**		
Diagnosis	IDC NST	Fr	36	9	45	0.99
		%	72.0%	18.0%	90.0%	
	ILC	Fr	4	1	5	
		%	8.0%	2.0%	10.0%	
Total		Fr	40	10	50	
		%	80.0%	20.0%	100.0%	
			COX-2 status		**Total**	**P-value**
			Positive	**Negative**		
In-situ component	Present	Fr	6	0	6	0.192
		%	12.0%	0.0%	12.0%	
	Absent	Fr	34	10	44	
		%	68.0%	20.0%	88.0%	
Total		Fr	40	10	50	
		%	80.0%	20.0%	100.0%	
			COX-2 status		**Total**	**P-value**
			Positive	**Negative**		
Histological grade	I	Fr	9	1	10	0.671
		%	18.0%	2.0%	20.0%	
	II	Fr	28	8	36	
		%	56.0%	16.0%	72.0%	
	III	Fr	3	1	4	
		%	6.0%	2.0%	8.0%	
Total		Fr	40	10	50	
		%	80.0%	20.0%	100.0%	
			COX-2 status		Total	P-value
			Positive	Negative		
ER receptor status	Positive	Fr	22	9	31	0.041
		%	44.0%	18.0%	62.0%	
	Negative	Fr	18	1	19	
		%	36.0%	2.0%	38.0%	
PR receptor status	Positive	Fr	20	9	29	0.031
		%	40.0%	18.0%	58.0%	
	Negative	Fr	20	1	21	
		%	40.0%	2.0%	42.0%	
HER2 receptor status	Positive	Fr	20	2	22	0.154
		%	40.0%	4.0%	44.0%	
	Negative	Fr	20	8	28	

		%	40.0%	16.0%	56.0%	
Total		Fr	40	10	50	
		%	80.0%	20.0%	100.0%	
			COX-2 status		**Total**	**P-value**
			Positive	**Negative**		
ER score	Negative	Fr	18	1	19	0.043
		%	36.0%	2.0%	38.0%	
	Mild	Fr	9	2	11	
		%	18.0%	4.0%	22.0%	
	Moderate	Fr	8	2	10	
		%	16.0%	4.0%	20.0%	
	Strong	Fr	5	5	10	
		%	10.0%	10.0%	20.0%	
PR score	Negative	Fr	20	1	21	0.001
		%	40.0%	2.0%	42.0%	
	Mild	Fr	14	1	15	
		%	28.0%	2.0%	30.0%	
	Moderate	Fr	3	5	8	
		%	6.0%	10.0%	16.0%	
	Strong	Fr	3	3	6	
		%	6.0%	6.0%	12.0%	
HER2 receptor status	Positive	Fr	20	2	22	0.154
		%	40.0%	4.0%	44.0%	
	Negative	Fr	20	8	28	
		%	40.0%	16.0%	56.0%	
Total		Fr	40	10	50	
		%	80.0%	20.0%	100.0%	
			COX-2 status		Total	P-value
			Positive	Negative		
Molecular classification	Luminal A and B	Fr	25	9	34	0.215
		%	50.0%	18.0%	68.0%	
	HER2 enriched	Fr	10	0	10	
		%	20.0%	0.0%	20.0%	
	TNBC	Fr	5	1	6	
		%	10.0%	2.0%	12.0%	
Total		Fr	40	10	50	
		%	80.0%	20.0%	100.0%	

For the association of COX-2 intensity with histological diagnosis of the patients with breast cancer of the study, there was no statistically significant association with p-value of 0.807. Similarly, there was also no statistically significant association between COX-2 intensity and *In-situ* component on histological assessment with p-value of 0.27. Meanwhile, for the association for COX-2 intensity with histological grade of breast cancer of the study. There was no statistically significant association with p-value of 0.65. Likewise, the association of hormone receptors status with COX-2 intensity showed no statistically significant association for all three (ER, PR and HER2 receptors) with COX-2 intensity with p-value>0.05. For the association of hormone receptors status with COX-2 intensity, there was a statistically significant association for PR expression with COX-2 intensity with p-value of 0.005, while there was no statistically significant association for ER and HER2 receptors with COX-2 expression with p-value<0.05. Assessment of the association for COX-2 intensity with molecular classification of breast cancer for patients of the study, there was no statistically significant association for the two of them with p-value of 0.366. As in table 3.

Table 3: The association of molecular classification with COX-2 score in breast cancer patients of the study

			COX-2 score			**Total**	**P-value**
			Negative	**Moderately positive**	**Strongly positive**		
Diagnosis	IDC NST	Fr	9	30	6	45	0.807
		%	18.0%	60.0%	12.0%	90.0%	
	ILC	Fr	1	3	1	5	
		%	2.0%	6.0%	2.0%	10.0%	
Total		Fr	10	33	7	50	
		%	20.0%	66.0%	14.0%	100.0%	
			COX-2 score			**Total**	**P-value**
			Negative	**Moderately positive**	**Strongly positive**		
In-situ component	Present	Fr	0	6	0	6	0.27
		%	0.0%	12.0%	0.0%	12.0%	
	Absent	Fr	10	27	7	44	
		%	20.0%	54.0%	14.0%	88.0%	
Total		Fr	10	33	7	50	
		%	20.0%	66.0%	14.0%	100.0%	

			COX-2 score			Total	P-value
			Negative	Moderately positive	Strongly positive		
Grade	I	Fr	1	7	2	10	0.653
		%	2.0%	14.0%	4.0%	20.0%	
	II	Fr	8	24	4	36	
		%	16.0%	48.0%	8.0%	72.0%	
	III	Fr	1	2	1	4	
		%	2.0%	4.0%	2.0%	8.0%	
Total		Fr	10	33	7	50	
		%	20.0%	66.0%	14.0%	100.0%	

			COX-2 score			Total	P-value
			Negative	Moderately positive	Strongly positive		
ER receptor status	Positive	Fr	9	18	4	31	0.129
		%	18.0%	36.0%	8.0%	62.0%	
	Negative	Fr	1	15	3	19	
		%	2.0%	30.0%	6.0%	38.0%	
PR receptor status	Positive	Fr	9	17	3	26	0.8
		%	18.0%	34.0%	6.0%	52.0%	
	Negative	Fr	1	16	4	24	
		%	2.0%	32.0%	8.0%	48.0%	
HER2 receptor status	Positive	Fr	2	17	3	22	0.237
		%	4.0%	34.0%	6.0%	44.0%	
	Negative	Fr	8	16	4	28	
		%	16.0%	32.0%	8.0%	56.0%	
Total		Fr	10	33	7	50	
		%	20.0%	66.0%	14.0%	100.0%	

			COX-2 score			Total	P-value
			Negative	Moderately positive	Strongly positive		
ER score	Negative	Fr	1	15	3	19	0.101
		%	2.0%	30.0%	6.0%	38.0%	
	Mild	Fr	2	6	3	11	
		%	4.0%	12.0%	6.0%	22.0%	
	Moderate	Fr	2	7	1	10	
		%	4.0%	14.0%	2.0%	20.0%	
	Strong	Fr	5	5	0	10	
		%	10.0%	10.0%	0.0%	20.0%	
PR score	Negative	Fr	1	16	4	21	0.005
		%	2.0%	32.0%	8.0%	42.0%	
	Mild	Fr	1	12	2	15	
		%	2.0%	24.0%	4.0%	30.0%	
	Moderate	Fr	5	3	0	8	
		%	10.0%	6.0%	0.0%	16.0%	
	Strong	Fr	3	2	1	6	
		%	6.0%	4.0%	2.0%	12.0%	
HER2 receptor status	Positive	Fr	2	17	3	22	0.237
		%	4.0%	34.0%	6.0%	44.0%	
	Negative	Fr	8	16	4	28	
		%	16.0%	32.0%	8.0%	56.0%	
Total		Fr	10	33	7	50	
		%	20.0%	66.0%	14.0%	100.0%	

			COX-2 score			Total	P-value
			Negative	Moderately positive	Strongly positive		
Molecular classification	Luminal A and B	Fr	9	20	5	34	0.366
		%	18.0%	40.0%	10.0%	68.0%	
	HER2 enriched	Fr	0	9	1	10	
		%	0.0%	18.0%	2.0%	20.0%	
	TNBC	Fr	1	4	1	6	
		%	2.0%	8.0%	2.0%	12.0%	
Total		Fr	10	33	7	50	
		%	20.0%	66.0%	14.0%	100.0%	

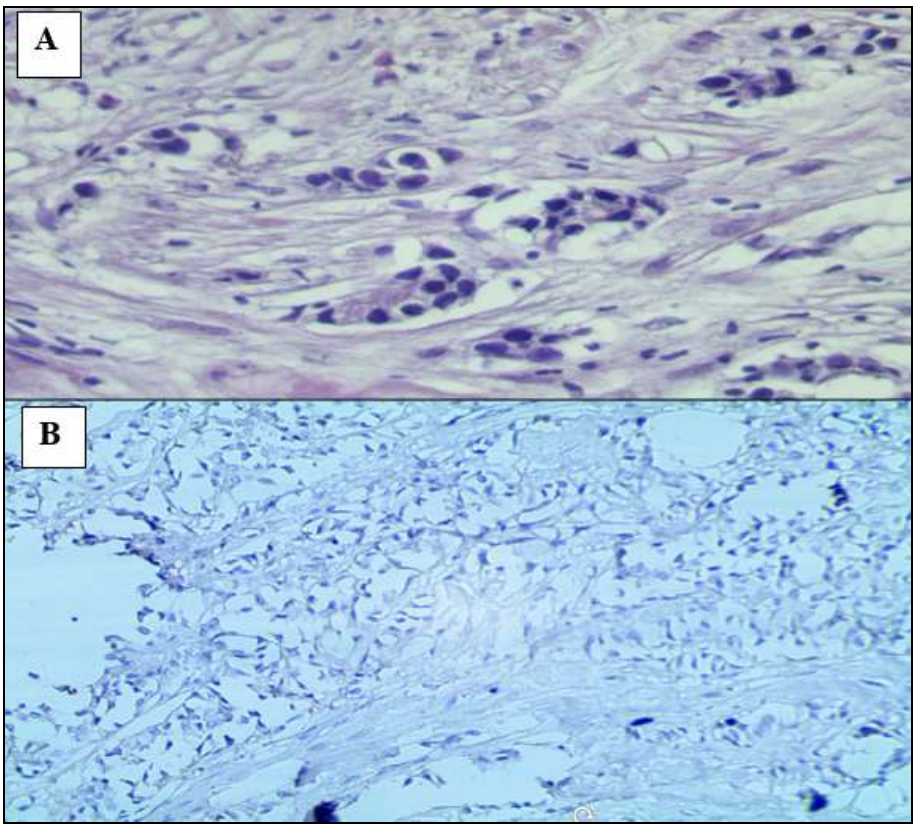

Fig 1: Invasive ductal carcinoma, grade I A. H&E stained slide sections (x40) B. Cox-2 stained slide section with (IHS score 0) (x20)

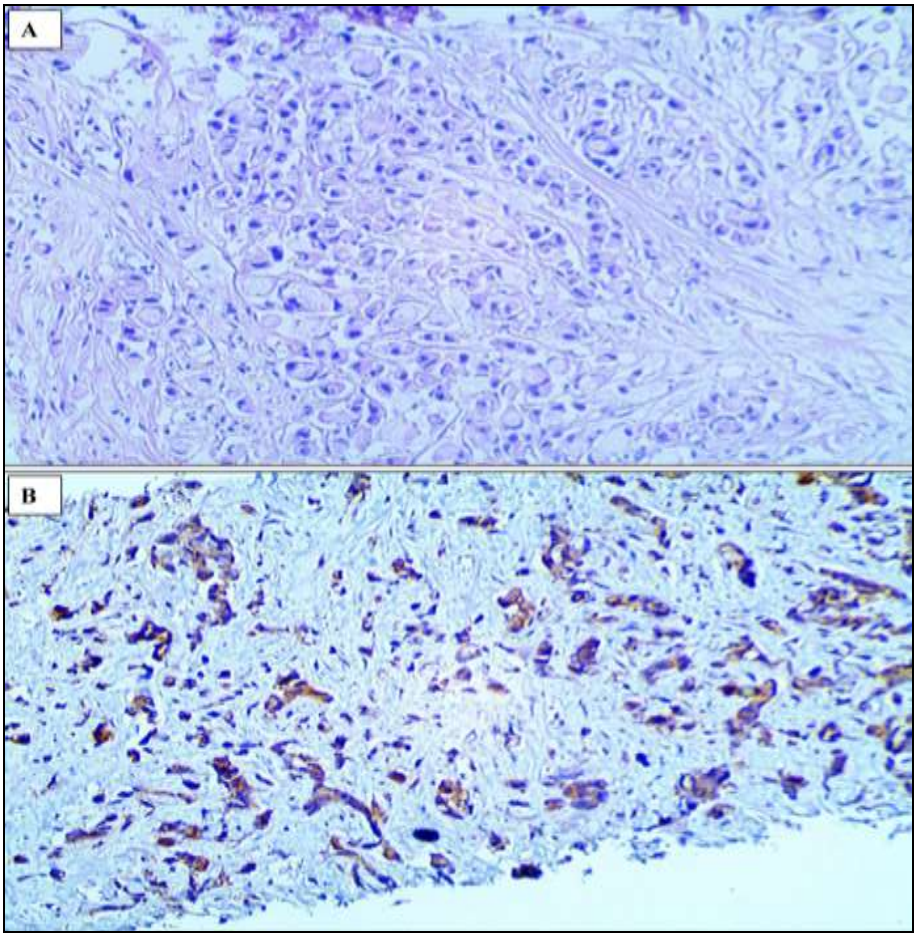

Fig 2: Invasive lobular carcinoma, Grade 2. A. H&E stained slide section (x20) B. Cox-2 stained slide section with (IHS score 2+) dark brown cytoplasm (x20)

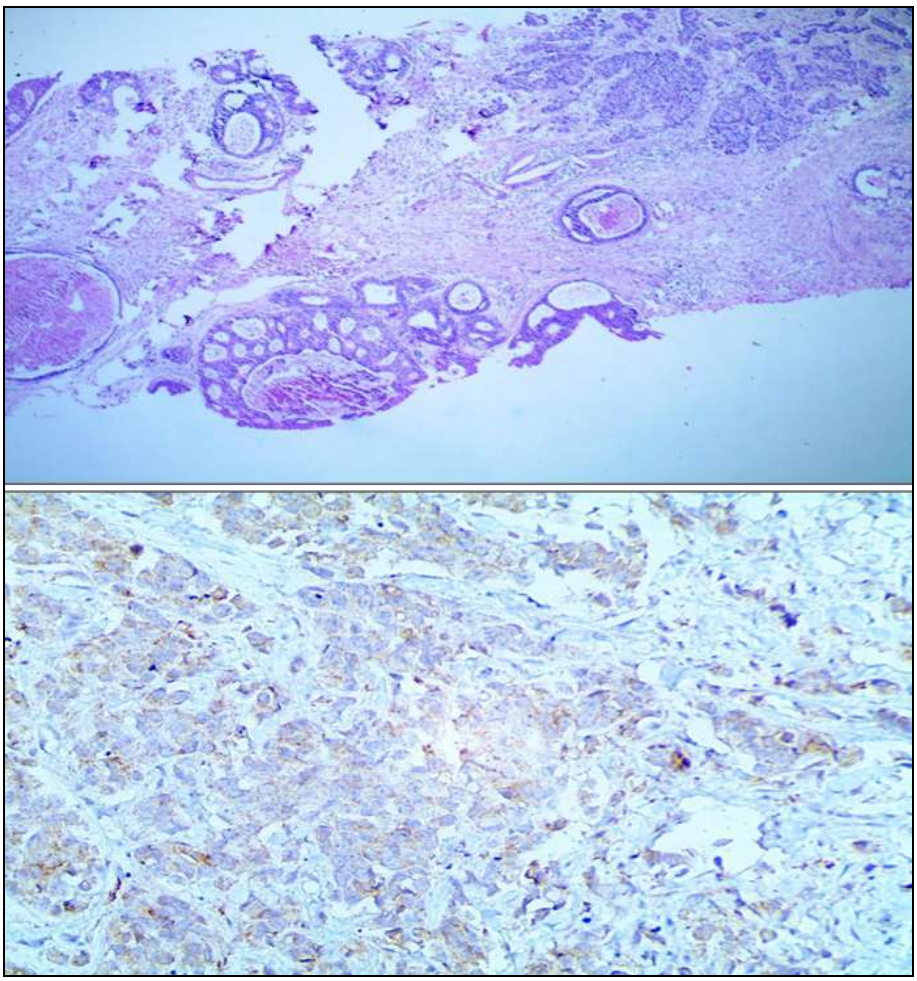

Fig 3: Invasive ductal carcinoma, grade 3 A. H&E stained slide section (x40) B. Cox-2 stained slide section with (IHS score 1+) dark brown cytoplasm (x40)

Discussion

The fundamental role of COX-2 enzymes in synthesizing prostaglandins (PGs) and thromboxanes from arachidonic acid underscores their potential significance in cancer development. Numerous studies over the past decades have consistently suggested that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of various cancers, including colon, lung, prostate, and breast cancer [10, 11]. *In vitro* experiments with cell lines have confirmed that NSAIDs and selective COX-2 inhibitors can inhibit breast cancer cell growth and carcinogenesis [12, 13]. Many studies have demonstrated COX-2's role in breast cancer initiation, growth, carcinogenesis, and metastasis, highlighting its potential as a prognostic factor [8, 13]. In this study, 40 (80%) of the patients exhibited positive COX-2 expression, aligning with findings by Guler *et al*. in Turkey, where 87% of breast cancer patients had COX-2 expression [14]. Other studies in Egypt and China reported COX-2 expression rates from 63% to 100% [8, 15]. However, some studies showed lower percentages, ranging from 37-56% [16], likely due to differences in cutoff values and scoring systems. The correlation between COX-2 expression and malignancy may involve excess PG biosynthesis associated with chronic inflammation, leading to genetic mutations, genome destabilization, uncontrolled proliferation, and resistance to apoptosis in tumor cells [17, 18]. In this study, 7 (14%) patients had strong COX-2 expression, and 33 (66%) had moderate expression, consistent with Harris *et al*., who associated moderate to strong COX-2 expression with decreased distant disease-free survival and aggressive breast cancer parameters [19]. The mean age of the patients was 53.56 years, ranging from 31 to 82 years, comparable to findings by Nassar *et al*. in Egypt (mean age 52 years) [8] and Jana *et al*. in India (mean age 50.78 years) [20]. There was no significant difference in COX-2 expression by age, suggesting COX-2 levels may not be strongly influenced by age [8]. Among the patients, 45 (90%) had Invasive Ductal Carcinoma of No Special Type (IDC-NST), and 5 (10%) had Invasive Lobular Carcinoma (ILC), consistent with other studies showing IDC-NST as the most common form of breast cancer [8, 20, 21]. No significant difference in COX-2 expression was found between histological types, aligning with findings by Barisic *et al*. [22] and other studies [8, 20, 23]. The presence of an *In-situ* component showed no significant difference in COX-2 expression, consistent with Nassar *et al*. [8]. Most patients had grade II breast cancer (72%), with no significant association between tumor grade and COX-2 expression, consistent with Nassar *et al*. and other studies [8, 24]. A significant inverse relationship was found between COX-2 expression and hormone receptor status, with ER and PR expression showing significant associations. This finding aligns with Abdel-rahman *et al*., Nassar *et al*., and other studies [8, 20, 25, 26]. ER and PR pathways may suppress COX-2 expression through various mechanisms, and high COX-2 levels correlate with more aggressive tumor phenotypes [25, 27]. For molecular classifications, although no significant association was found, 50% of Luminal A and B subtypes showed positive COX-2 expression, while all HER2/neu patients had positive expression and one TNBC patient showed negative COX-2 expression. This aligns with

Serra *et al*. [7], suggesting hormonal tumors may exhibit lower COX-2 expression due to different molecular pathways [28, 29].

Conclusion

A statistically significant inverse relationship exists between COX-2 expression and hormone receptor status, particularly with estrogen and progesterone receptors, indicating potential prognostic implications, indicating its role as a predictive biomarker for breast cancer aggressive nature.

Conflict of Interest

Not available

Financial Support

Not available

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Ministry of Health of Iraq. Iraqi cancer registry [Internet]. [cited 2024 Jan 7]. Available from: https://moh.gov.iq/upload/2991322580.pdf
3. Maas P, Barrdahl M, Joshi AD, Auer PL, Gaudet MM, Milne RL, *et al*. Breast cancer risk from modifiable and nonmodifiable risk factors among white women in the United States. JAMA Oncol. 2016;2(10):1295-302.
4. Makki J. Diversity of breast carcinoma: histological subtypes and clinical relevance. Clin Med Insights Pathol. 2015;8.S31563.
5. Cimino-Mathews A. Novel uses of immunohistochemistry in breast pathology: interpretation and pitfalls. Mod Pathol. 2021;34:62-77.
6. Hugo HJ, Saunders C, Ramsay RG, Thompson EW. New insights on COX-2 in chronic inflammation driving breast cancer growth and metastasis. J Mammary Gland Biol Neoplasia. 2015;20:109-19.
7. Serra KP, Peres RMR, Sarian LO, Vassallo J, Pinto GA, de Paiva Silva GR, *et al*. Cyclooxygenase-2 (COX-2) and p53 protein expression are interdependent in breast cancer but not associated with clinico-pathological surrogate subtypes, tumor aggressiveness, and patient survival. Acta Histochem. 2016;118(2):176-82.
8. Nassar MIA, Bebars SM, Said RMS, Mustafa TMA. Immunohistochemical expression of cyclooxygenase-2 (COX-2) in breast cancer. Egypt J Hosp Med. 2019;75(3):2397-405.
9. Dobrescu A, Chang M, Kirtani V, Turi GK, Hennawy R, Hindenburg AA. Study of estrogen receptor and progesterone receptor expression in breast ductal carcinoma in situ by immunohistochemical staining in ER/PgR-negative invasive breast cancer. Int Sch Res Not. 2011;2011.
10. Rolland PH, Martin PM, Jacquemier J, Rolland AM, Toga M. Prostaglandin in human breast cancer: evidence suggesting that an elevated prostaglandin production is a marker of high metastatic potential for neoplastic cells. J Natl Cancer Inst. 1980;64(5):1061-70.
11. Castelao JE, Bart RD III, DiPerna CA, Sievers EM, Bremner RM. Lung cancer and cyclooxygenase-2. Ann Thorac Surg. 2003;76(4):1327-35.
12. Kim MJ, Kim HS, Lee SH, Yang Y, Lee MS, Lim JS. NDRG2 controls COX-2/PGE2-mediated breast cancer cell migration and invasion. Mol Cells. 2014;37(10):759-66.
13. Singh B, Irving LR, Tai K, Lucci A. Overexpression of COX-2 in celecoxib-resistant breast cancer cell lines. J Surg Res. 2010;163(2):235-43.
14. Güler SA, Uğurlu MÜ, Kaya H, Şen S, Nazlı Y, Güllüoğlu BM. Impact of cyclooxygenase-2 over-expression on the prognosis of breast cancer patients. Turk J Surgery Ulusal Cerrahi Derg. 2016;32(2):81-6.
15. Zhang XH, Huang DP, Guo GL, Chen GR, Zhang HX, Wan L, *et al*. Coexpression of VEGF-C and COX-2 and its association with lymphangiogenesis in human breast cancer. BMC Cancer. 2008;8:1-8.
16. Xu F, Li M, Zhang C, Cui J, Liu J, Li J, *et al*. Clinicopathological and prognostic significance of COX-2 immunohistochemical expression in breast cancer: a meta-analysis. Oncotarget. 2017;8(4):6003-15.
17. Regulski M, Regulska K, Prukała W, Piotrowska H, Stanisz B, Murias M. COX-2 inhibitors: a novel strategy in the management of breast cancer. Drug Discov Today. 2016;21(4):598-615.
18. Lin C, Zhang J. Inflammasomes in inflammation-induced cancer. Front Immunol. 2017;8:271.
19. Harris RE, Casto BC, Harris ZM. Cyclooxygenase-2 and the inflammogenesis of breast cancer. World J Clin Oncol. 2014;5(4):677-92.
20. Jana D, Sarkar DK, Ganguly S, Saha S, Sa G, Manna AK, *et al*. Role of cyclooxygenase 2 (COX-2) in prognosis of breast cancer. Indian J Surg Oncol. 2014;5:59-65.
21. Rakha EA, Badve S, Eusebi V, Reis-Filho JS, Fox SB, Dabbs DJ, *et al*. Breast lesions of uncertain malignant nature and limited metastatic potential: proposals to improve their recognition and clinical management. Histopathology. 2016;68(1):45-56.
22. Barısık NO, Keser SH, Gul AE, Sensu S, Kandemir NO, Kucuk HF, *et al*. The value of COX-2 expression in the prognostic parameters of invasive ductal carcinoma of the breast. Med Oncol. 2011;28:703-8.
23. Turashvili G, Brogi E. Tumor heterogeneity in breast cancer. Front Med. 2017;4:227.
24. Misron NA, Looi LM, Mustapha NRN. Cyclooxygenase-2 expression in invasive breast carcinomas of no special type and correlation with pathological profiles suggest a role in tumorigenesis rather than cancer progression. Asian Pac J Cancer Prev. 2015;16(4):1553-8.
25. Abdel-rahman FZ, Zaky AH, Zedan A, Elsaba TM, Gabr A. COX-2 (Cyclooxygenase 2) as a prognostic marker in breast cancer. SVU Int J Med Sci. 2021;4(2):219-30.
26. Kargi A, Uysal M, Bozcuk H, Coskun HS, Savas B, Ozdogan M. The importance of COX-2 expression as a prognostic factor in early breast cancer. J Buon. 2013;18(3):579-84.
27. Desai SJ, Prickril B, Rasooly A. Mechanisms of phytonutrient modulation of cyclooxygenase-2 (COX-2) and inflammation related to cancer. Nutr Cancer. 2018;70(3):350-75.
28. Jiang X, Shapiro DJ. The immune system and inflammation in breast cancer. Mol Cell Endocrinol. 2014;382(1):673-82.

29. Basu S, Sarkar DK. Prognostication in breast cancer. In: Breast Diseases. CRC Press; 2024. p. 141-5.

How to Cite This Article
Abes NK, Karbel HA. Prognostic values of cyclooxygenase-2 in invasive breast cancer. International Journal of Clinical and Diagnostic Pathology 2024; 7(3): 258-266.