



IMMUNOHISTOCHEMICAL EXPRESSION OF CXCR2 IN BREAST CARCINOMA AND ITS ASSOCIATION WITH ER, PR AND HER2/NEU STATUS: A CROSS-SECTIONAL STUDY FROM A TERTIARY CARE CENTRE

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ABSTRACT

Background: CXCR2 chemokine receptor-2 (CXCR2) has emerged as a candidate cancer stem-cell related biomarker in breast carcinoma, with reported roles in epithelial–mesenchymal transition, angiogenesis, metastasis and chemoresistance. However, clinicopathological data on CXCR2 expression in routine breast carcinoma specimens remain limited. The present study evaluated CXCR2 immunohistochemical expression in breast carcinoma and assessed its association with estrogen receptor (ER), progesterone receptor (PR), HER2/neu status and clinicopathological parameters.

Methods: This cross-sectional analytical study was carried out in the Department of Pathology, Era's Lucknow Medical College and Hospital, Lucknow, India, over 20 months (April 2020 to November 2021). Fifty newly diagnosed, histopathologically confirmed cases of breast carcinoma were included. Formalin-fixed paraffin-embedded sections were stained with hematoxylin and eosin for diagnosis and grading. Immunohistochemistry was performed for ER, PR, HER2/neu and CXCR2. ER and PR were interpreted as positive or negative; HER2/neu was interpreted according to standard immunohistochemical criteria; CXCR2 immunoreactivity was categorized as low expression (score <6) or high expression (score ≥6). Associations with age, AJCC clinical stage and Nottingham histological grade were analyzed using chi-square testing.

Results: Of the 50 patients, 24 (48.0%) were aged <45 years and 26 (52.0%) were aged ≥45 years. Clinical stage II was the most common stage (32/50, 64.0%), and Nottingham grade II was the predominant histological grade (23/50, 46.0%). ER positivity, PR positivity and HER2/neu positivity were observed in 17 (34.0%), 12 (24.0%) and 13 (26.0%) cases, respectively. High CXCR2 expression was identified in 29 (58.0%) cases, while 21 (42.0%) showed low expression. High CXCR2 expression was significantly associated with age ≥45 years (76.9% vs 37.5% in patients <45 years; $\chi^2=7.9$, $p=0.004$) and higher Nottingham grade (grade I: 12.5%, grade II: 73.9%, grade III: 81.8%; $\chi^2=18.25$, $p=0.0001$). CXCR2 expression increased with advancing clinical stage, but the association was not statistically significant ($\chi^2=3.2$, $p=0.19$). HER2/neu expression showed a significant association with clinical stage ($\chi^2=10.7$, $p=0.01$), whereas ER and PR did not show significant associations with age, stage or grade.

Conclusions: CXCR2 is frequently expressed in breast carcinoma and demonstrates significant association with older age and higher histological grade. These findings support a potential role for CXCR2 as a biomarker of tumor aggressiveness and a candidate prognostic stem-cell related marker in breast carcinoma. Larger multicentric studies with survival analysis and molecular validation are required to confirm its clinical utility.

Keywords: Breast Carcinoma, Cxcr2, Immunohistochemistry, Er, Pr, Her2/Neu, Clinicopathological Correlation, Cancer Stem Cell Marker.



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INTRODUCTION

Breast carcinoma is the most common malignancy in women worldwide and remains a major cause of cancer-related mortality [1,2]. It is a biologically heterogeneous disease with marked intertumoral variability in morphology, molecular profile, therapeutic response and clinical outcome [2–4]. In routine practice, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2/neu) status are integral to breast cancer classification, prognostication and treatment selection [3–6]. However, conventional surrogate molecular markers do not fully explain tumor aggressiveness, metastatic potential or therapeutic resistance in all cases.

Cancer stem-like cells have been increasingly implicated in tumor initiation, progression, metastasis, chemoresistance and recurrence in breast carcinoma [7,8]. Among the candidate molecules linked to this stem-like phenotype, CXC chemokine receptor-2 (CXCR2) has emerged as a potentially relevant biomarker in breast cancer, particularly in aggressive and triple-negative subtypes [9–13]. CXCR2 is a G-protein-coupled receptor for ELR-positive CXC chemokines and has been implicated in tumor-promoting inflammation, angiogenesis, invasion, migration and metastatic dissemination [10,11,13]. Experimental studies have shown that CXCR2 signaling can enhance epithelial–mesenchymal transition, support cancer stem-cell maintenance, suppress apoptosis and contribute to chemoresistance in breast carcinoma [9–13]. CXCR2 has also been proposed as a cancer stem-like cell marker in triple-negative breast carcinoma, further increasing interest in its prognostic and therapeutic relevance [9].

Although molecular and experimental evidence supports a role for CXCR2 in breast cancer biology, immunohistochemical data correlating CXCR2 expression with routine clinicopathological parameters and established surrogate molecular markers in human breast carcinoma remain limited [9–13]. The present study was therefore undertaken to evaluate CXCR2 expression in breast carcinoma and to determine its association with ER, PR and HER2/neu status, as well as age, clinical stage and histological grade.

MATERIALS AND METHODS

Study design and setting

This cross-sectional analytical study was conducted in the Department of Pathology, Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India, over a period of 20 months from April 2020 to November 2021.

Study population

A total of 50 patients aged 27–70 years with clinically suspected and histopathologically confirmed breast carcinoma were included. Breast tissue specimens were received from the Department of General Surgery in the form of mastectomy or wedge biopsy specimens. Written informed consent was obtained from all participants, and the study was approved by the institutional ethics committee.

Inclusion criteria

- (1) Newly diagnosed and histopathologically confirmed cases of breast carcinoma.
- (2) Availability of adequate clinicopathological details and formalin-fixed paraffin-embedded tissue for immunohistochemistry.

Exclusion criteria

- (1) Cases with another concurrent malignancy.
- (2) Previously treated or currently treated cases of breast carcinoma likely to interfere with marker expression.

Histopathological evaluation

All tissue specimens were fixed in 10% neutral buffered formalin and processed by standard paraffin-embedding techniques. Hematoxylin and eosin-stained sections were examined for histopathological diagnosis and grading. Histological typing was performed according to the WHO Classification of Breast Tumours, 5th edition (2019) [14], and histological grading was carried out using the Nottingham modification of the Scarff–Bloom–Richardson grading system [15,16].

Immunohistochemistry

Immunohistochemical staining was performed on formalin-fixed paraffin-embedded tissue sections using standard laboratory protocols. The primary antibodies used were anti-ER (mouse monoclonal, ready to use), anti-PR (mouse monoclonal, ready to use), anti-HER2/neu (rabbit monoclonal, ready to use) and anti-CXCR2 (rabbit polyclonal, 1:50 dilution; Immunotag, St. Louis, MO, USA). Antigen retrieval was performed using EDTA-Tris buffer (pH 9.0), followed by incubation with the primary antibody, secondary detection using HRP-based detection chemistry and chromogenic visualization with diaminobenzidine (DAB). Appropriate positive and negative controls were included in each run.

Interpretation of immunostaining

ER and PR expression were interpreted on the basis of nuclear staining in tumor cells according to the ASCO/CAP guideline recommendations for hormone receptor testing in breast cancer [17,18].

HER2/neu expression was interpreted according to the ASCO/CAP guideline recommendations for HER2 testing in breast cancer [19,20]. CXCR2 immunoreactivity was assessed semiquantitatively and categorized as low expression (score <6) or high expression (score ≥6), as described previously [9,10].

Clinicopathological variables

The following variables were recorded: age (<45 years or ≥45 years), AJCC clinical stage (I–III) and Nottingham histological grade (I–III). Clinical staging was assigned according to the American Joint Committee on Cancer (AJCC) staging system, 8th edition [21]. ER, PR, HER2/neu and CXCR2 expression were correlated with these clinicopathological parameters.

Statistical analysis : Data were entered into Microsoft Excel and analyzed using chi-square testing. A p value <0.05 was considered statistically significant.

RESULTS

A total of 50 histopathologically confirmed cases of breast carcinoma were studied. Patients ranged in age from 27 to 70 years; 24 (48.0%) were younger than 45 years and 26 (52.0%) were aged 45 years or above. Clinical stage II was the most frequent stage, accounting for 32 cases (64.0%), followed by stage III in 13 cases (26.0%) and stage I in 5 cases (10.0%). On histological grading, Nottingham grade II was the predominant category (23/50, 46.0%), followed by grade I (16/50, 32.0%) and grade III (11/50, 22.0%).

ER positivity was observed in 17/50 cases (34.0%), PR positivity in 12/50 cases (24.0%) and HER2/neu positivity in 13/50 cases (26.0%). CXCR2 high expression (score ≥6) was seen in 29/50 cases (58.0%), while 21/50 cases (42.0%) showed low expression.

Association of ER and PR with clinicopathological parameters ER positivity was more frequent in

patients aged <45 years (11/24, 45.8%) than in those aged ≥45 years (6/26, 23.1%), but the association was not statistically significant ($\chi^2=2.58$, $p=0.89$). ER expression also showed no significant association with clinical stage ($\chi^2=1.67$, $p=0.43$) or histological grade ($\chi^2=0.36$, $p=0.83$). Similarly, PR expression showed no significant association with age ($\chi^2=0.02$, $p=0.873$), clinical stage ($\chi^2=1.65$, $p=0.436$) or histological grade ($\chi^2=1.16$, $p=0.558$). Association of HER2/neu with clinicopathological parameters HER2/neu positivity was identified in 8/24 patients (33.3%) aged <45 years and 5/26 patients (19.2%) aged ≥45 years, without significant age association ($\chi^2=0.7$, $p=0.41$). HER2/neu showed a significant association with clinical stage ($\chi^2=10.7$, $p=0.01$). HER2/neu positivity was seen in 3/5 stage I cases (60.0%), 4/32 stage II cases (12.5%) and 7/13 stage III cases (53.8%). No significant association was observed between HER2/neu expression and histological grade ($\chi^2=0.17$, $p=0.12$).

Association of CXCR2 with clinicopathological parameters High CXCR2 expression was significantly more frequent in patients aged ≥45 years (20/26, 76.9%) than in those aged <45 years (9/24, 37.5%) ($\chi^2=7.9$, $p=0.004$). CXCR2 high expression was present in 1/5 stage I cases (20.0%), 20/32 stage II cases (62.5%) and 8/13 stage III cases (61.5%); although the proportion increased with advancing stage, the association did not reach statistical significance ($\chi^2=3.2$, $p=0.19$). In contrast, CXCR2 expression demonstrated a strong association with histological grade ($\chi^2=18.25$, $p=0.0001$): high expression was seen in 2/16 grade I cases (12.5%), 17/23 grade II cases (73.9%) and 9/11 grade III cases (81.8%).

Taken together, the data suggest that CXCR2 expression is enriched in biologically aggressive breast carcinomas, particularly in older patients and tumors with higher histological grade. [5]

Table 1. Clinicopathological profile and immunohistochemical marker expression in the study cohort

Variable	Category	n (%)
Age (years)	<45	24 (48.0)
	≥45	26 (52.0)
Clinical stage	I	5 (10.0)
	II	32 (64.0)
	III	13 (26.0)
Histological grade	I	16 (32.0)
	II	23 (46.0)
	III	11 (22.0)
ER expression	Positive	17 (34.0)
	Negative	33 (66.0)
PR expression	Positive	12 (24.0)
	Negative	38 (76.0)
HER2/neu expression	Positive	13 (26.0)

	Negative	37 (74.0)
CXCR2 expression	High	29 (58.0)
	Low	21 (42.0)

Table 2. Association of ER, PR, HER2/neu expression with clinicopathological parameters

Variable	Category	ER positive n (%)	ER negative n (%)	p value	PR positive n (%)	PR negative n (%)	p value	HER2 positive n (%)	HER2 negative n (%)	p value
Age (years)	<45	11 (45.8)	13 (54.2)	0.108 *	6 (25.0)	18 (75.0)	0.873	8 (33.3)	16 (66.7)	0.410
	≥45	6 (23.1)	20 (76.9)		6 (23.1)	20 (76.9)		5 (19.2)	21 (80.8)	
Clinical stage	I	3 (60.0)	2 (40.0)	0.430	2 (40.0)	3 (60.0)	0.436	3 (60.0)	2 (40.0)	0.010
	II	10 (31.3)	22 (68.7)		7 (21.9)	25 (78.1)		4 (12.5)	28 (87.5)	
	III	4 (30.8)	9 (69.2)		3 (23.1)	10 (76.9)		6 (46.2)	7 (53.8)	
Histologic al grade	I	6 (37.5)	10 (62.5)	0.830	6 (37.5)	10 (62.5)	0.558	4 (25.0)	12 (75.0)	0.120
	II	8 (34.8)	15 (65.2)		4 (17.4)	19 (82.6)		6 (26.1)	17 (73.9)	
	III	3 (27.3)	8 (72.7)		2 (18.2)	9 (81.8)		3 (27.3)	8 (72.7)	

Table 3. Association of CXCR2 expression with clinicopathological parameters

Variable	Category	CXCR2 high n (%)	CXCR2 low n (%)	p value
Age (years)	<45	9 (37.5)	15 (62.5)	0.004
	≥45	20 (76.9)	6 (23.1)	
Clinical stage	I	1 (20.0)	4 (80.0)	0.190
	II	20 (62.5)	12 (37.5)	
	III	8 (61.5)	5 (38.5)	
Histological grade	I	2 (12.5)	14 (87.5)	0.0001
	II	17 (73.9)	6 (26.1)	
	III	10 (90.9)	1 (9.1)	

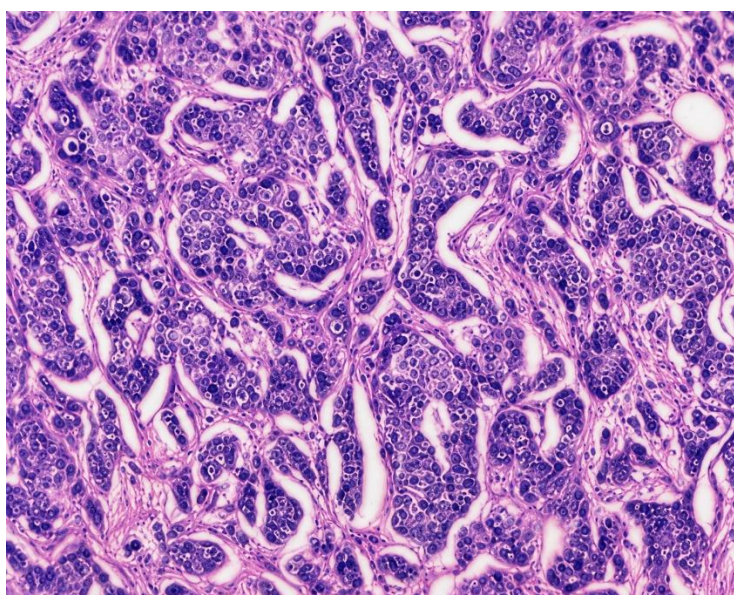


Figure 1 - Invasive Ductal Carcinoma Grade II (40X)

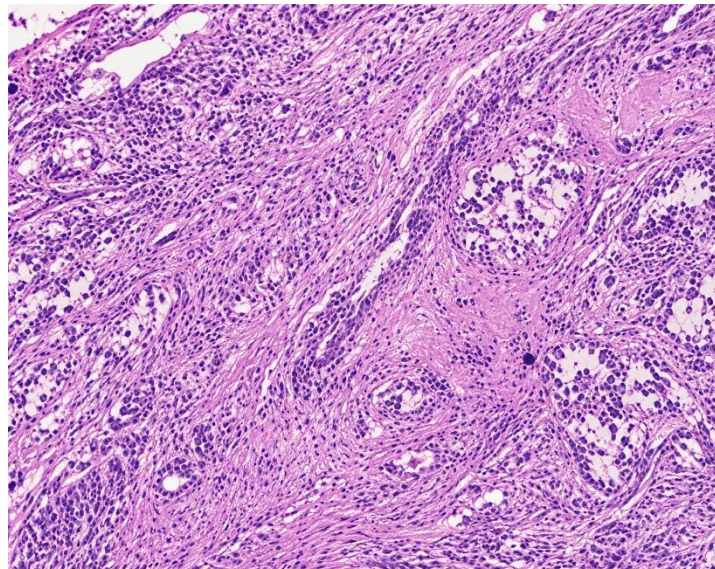


Figure 2: Invasive Ductal Carcinoma Grade III (10X)

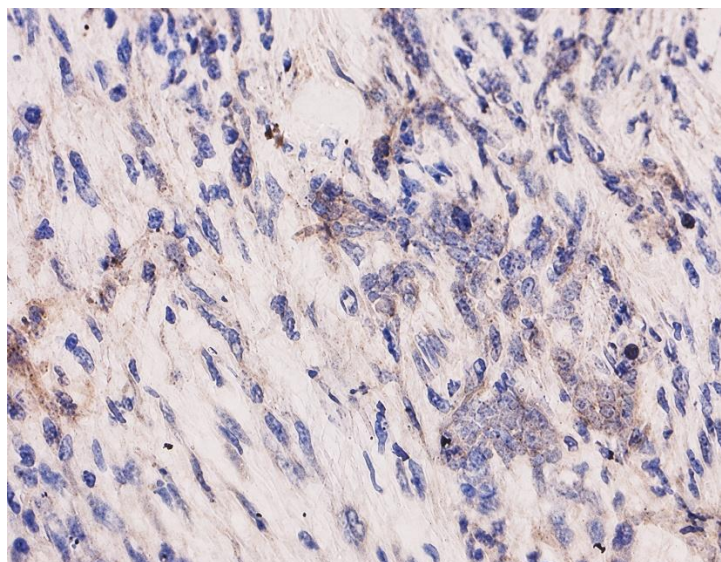


Figure 3: CXCR2 Low Expression Stage I and Grade-I Invasive ductal carcinoma (40x)

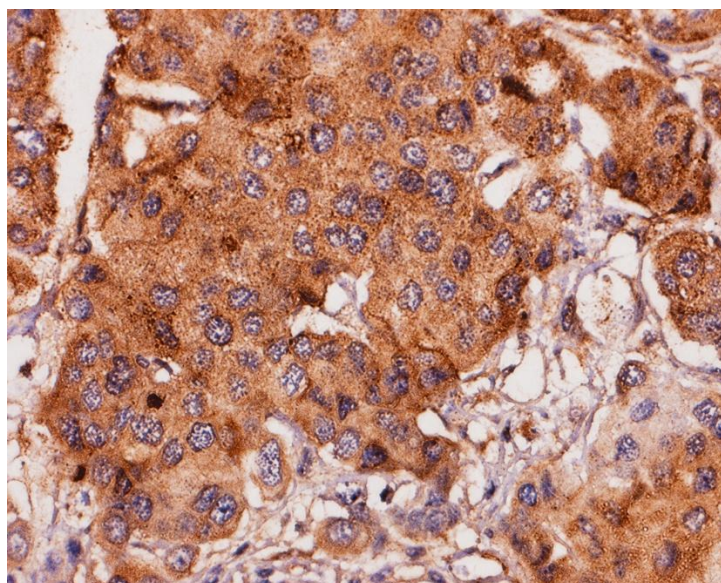


Figure 4: CXCR2 High Expression Stage-III and Grade-III,

Invasive Ductal Carcinoma (40X)

DISCUSSION

The present study evaluated the immunohistochemical expression of CXCR2 in breast carcinoma and its association with routine surrogate molecular markers and clinicopathological parameters. The most notable finding was the frequent expression of CXCR2, with high expression in 58% of cases, and its significant association with older age and higher histological grade. These findings support the concept that CXCR2 is linked to biologically aggressive tumor behavior in breast carcinoma [9–13,22].

In the present cohort, ER, PR and HER2/neu positivity rates were 34%, 24% and 26%, respectively. ER and PR did not show significant associations with age, stage or histological grade, whereas HER2/neu demonstrated a significant association with clinical stage. These findings should be interpreted cautiously because of the modest sample size and uneven stage distribution; however, they are in keeping with the recognized biological heterogeneity of HER2-driven breast carcinoma and the variable clinicopathological behavior of HER2-positive tumors [3–6,19,20,23,24].

The central observation of this study concerns CXCR2. High CXCR2 expression was significantly more frequent in patients aged ≥ 45 years and showed a striking increase across histological grades, from 12.5% of grade I tumors to 73.9% of grade II tumors and 81.8% of grade III tumors. This strong association with higher Nottingham grade suggests that CXCR2 expression parallels increasing tumor dedifferentiation and aggressiveness. Although CXCR2 expression increased numerically with advancing clinical stage,

the association did not reach statistical significance, likely because of the limited sample size and the predominance of stage II cases. Similar observations linking CXCR2 signaling with aggressive tumor biology, metastatic progression and adverse prognosis in breast cancer have been reported in previous studies [9–13,22,25].

These findings are biologically plausible. CXCR2 signaling has been implicated in tumor-promoting inflammation, angiogenesis, invasion, metastatic dissemination and resistance to therapy [10,11,13,22,25]. In breast cancer specifically, CXCR2 has been shown to promote metastasis and chemoresistance and has also been proposed as a marker of cancer stem-like cells, particularly in triple-negative disease [7–13,22]. Experimental studies further suggest that the CXCR2 axis can facilitate epithelial–mesenchymal transition and maintain stemness-related phenotypes, thereby contributing to aggressive tumor biology [9–13,22,25,26]. Within this framework, the association of high CXCR2 expression with higher histological grade in the present study reinforces the hypothesis that CXCR2 may serve as a marker of biologically aggressive breast carcinoma.

Another notable observation from the present dataset is the tendency for high CXCR2 expression in triple-negative breast carcinoma cases. This is clinically relevant because triple-negative tumors are often enriched for stem-like phenotypes and are associated with aggressive behavior, early metastasis and limited targeted treatment options [7–9,27,29]. The previously published study by Wang et al., which identified CXCR2 as a cancer stem-like cell marker in triple-negative breast carcinoma, provides additional biological support for this interpretation [9].

The present study has several limitations. It was conducted at a single center and included only 50 cases. No follow-up, survival analysis or treatment-response data were available, precluding formal prognostic assessment. In addition, CXCR2 was evaluated by immunohistochemistry without parallel molecular validation. The threshold used for high versus low expression also requires validation in larger independent cohorts. Despite these limitations, the study provides practical histopathology-based evidence that CXCR2 expression is associated with adverse clinicopathological features and merits further investigation. Similar limitations, including lack of standardized scoring thresholds and the need for larger validation cohorts, have also been highlighted in biomarker-oriented breast cancer studies [22,25,29].

Overall, the present findings suggest that CXCR2 may serve as a useful adjunct biomarker in breast carcinoma, particularly for identifying tumors with higher histological grade and potentially more aggressive biological behavior. Larger multicentric studies incorporating outcome analysis and molecular validation are needed to define the precise prognostic and therapeutic role of CXCR2 in breast cancer [9–13,22,25,27,29].

CONCLUSION

In summary, CXCR2 was frequently expressed in breast carcinoma, and high CXCR2 expression showed significant association with older age and higher Nottingham histological grade. HER2/neu expression was significantly associated with clinical stage, whereas ER and PR did not show significant associations with the clinicopathological variables studied. The enrichment of high CXCR2 expression in higher-grade tumors supports its potential role as a predictive and prognostic cancer stem-cell related biomarker in breast carcinoma [4-6,15-19]. Larger multicentric studies with outcome data and molecular validation are required before CXCR2 can be incorporated into routine risk stratification or targeted therapeutic algorithms.

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