RESEARCH ARTICLE

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Comparison of GATA-3, Mammaglobin and GCDFP-15 Expression in Primary, Metastatic and Triple Negative Breast Carcinomas: An Indian Scenario

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Abstract

Background and objective: Mammaglobin and GCDFP-15 are traditional immunohistochemistry (IHC) markers utilized to recognize metastasis of breast carcinoma in an unknown primary. GATA-3 is increasingly being used as a marker of primary breast origin. This study was done to evaluate and compare GATA-3 with GCDFP-15 and Mammaglobin in invasive primary including metastatic and triple negative breast carcinomas. **Methods:** Immunohistochemistry for GATA-3, GCDFP-15 and Mammaglobin was applied on 100 cases of primary breast carcinomas, including 20 triple negative cases and 30 cases of metastatic breast carcinomas. Staining scores were given for each marker by multiplying the percentage of positive tumor cells by the intensity of staining (1+, 2+ or 3+), with scores ranging from 0 to 300. Staining score of 1 or more was considered positive. **Results:** GATA-3 was expressed in 92% of primary, 80% of metastatic and 60% of triple negative breast carcinomas, with an average staining score of 270. Mammaglobin was expressed in 68% of primary, 56.6% of metastatic and 25% of triple negative breast carcinomas, with an average staining score of 180. GCDFP-15 was expressed in 48% of primary, 26.6% of metastatic and 05% of breast carcinomas, with an average staining score of 60. GATA-3 demonstrated to have higher staining score (average of 270) than other two markers in maximum number of cases. **Conclusion:** GATA-3 has a higher sensitivity and increased staining scores in primary breast carcinomas, metastatic breast carcinomas as well as in triple negative breast carcinomas.

Keywords: Breast carcinoma- GATA-3- Mammaglobin- GCDFP-15

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Introduction

Breast carcinoma is the most common malignancy in females (Jemal et al., 1999). For determination of primary breast origin in tumors of unknown primary, estrogen receptor (ER), progesterone receptor (PgR), gross cystic disease fluid protein 15 (GCDFP-15) and mammaglobin are the breast specific immunomarkers traditionally used (Bhargava et al., 2007; Darb-Esfahani et al., 2014; Hattori et al., 2015; Hou et al., 2017; Zehentner and Carter, 2004). However, 10-20% of breast carcinomas are triple negative breast carcinomas (TNBC), lacking expression of ER, PgR and Her2/neu. In developing countries like India, the number is as high as 31% (Sandhu et al., 2016). The other two markers, i.e, GCDFP-15 and mammaglobin suffer from low sensitivities (35% to 55% for GCDFP-15 and 65% to 75% for mammaglobin) (Liu et al., 2014). Their sensitivity in ER-negative breast carcinomas is also being reported as low (15% for GCDFP-15 and 35% for Mammaglobin) (Hou et al., 2017).

GATA binding protein-3 (GATA-3), a 48 kDa protein is a zinc finger transcription factors encoded by gene located on chromosome 10p15 (Ni et al., 2018). Other than being a transcriptional factor for T-cell development, it has an important role in mammary gland morphogenesis and differentiation of luminal cells in adult mammary gland (Asch-Kendrick and Cimino-Mathews, 2016; El Hag et al., 2017; Liu et al., 2014). GATA binding protein 3 (GATA-3) is increasingly being used as a marker of primary breast origin (El Hag et al., 2017; Ni et al., 2015). Although it is expressed in many other tumors like squamous cell carcinoma, basal cell carcinoma, skin adnexal tumors, salivary gland tumors; it is a sensitive marker only for breast and urothelial carcinoma (Ni et

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al., 2018). GATA-3 is known to have a high expression in luminal types of breast cancer and is associated with ER expression (Hou et al., 2017).

Since breast cancer biology is influenced by genetic and environmental factors, this study was undertaken to evaluate GATA-3, GCDFP-15 and mammaglobin expression in primary breast carcinomas, triple negative breast carcinomas and metastatic breast carcinomas in a tertiary care center in India, and to see the expression of these markers in the Indian population.

Materials and Methods

The study was conducted at the All India Institute of Medical Sciences (AIIMS), Jodhpur, after gaining approval from the institutional board ethics committee (certificate number: AIIMS/IEC/2017/750). This was a retrospective as well as prospective study which included 100 cases of primary breast carcinomas, including 20 triple negative cases, and 30 cases of metastatic breast carcinomas. The primary breast carcinoma cases included core needle biopsies, incision biopsies, wedge biopsies and modified radical mastectomy specimens. Out of the 30 metastatic carcinomas, 25 cases were of metastasis to axillary lymph nodes, 2 cases of metastasis to cervical lymph nodes, 2 cases of metastasis to supraclavicular lymph node and 1 case of abdominal deposits in a follow-up case of breast carcinoma. Formalin fixed paraffin embedded (FFPE) tissue was used for all cases. The estrogen receptor (ER), progesterone receptor (PgR) and Her2/neu status was known for all the primary cases as part of routine laboratory histopathology report.

Immunohistochemistry (IHC) for GATA-3 was performed using mouse monoclonal antibody (clone: L50-823, ready to use, Biocare medical). Mammaglobin staining was performed using mouse monoclonal antibody (clone: 304-1A5, ready to use, Dako) and GCDFP-15 staining was performed using mouse monoclonal antibody (clone: 23A3, ready to use, Dako). IHC was performed on Leica Bondmax. Details of the primary antibodies, pretreatment and detection system are indicated in Table 1. In all the metastatic breast carcinoma cases, IHC was put on the metastatic site.

Nuclear positivity for GATA-3 and cytoplasmic staining for GCDFP-15 and mammaglobin was considered positive (Figure 1). Staining score was calculated for each marker by multiplying the intensity of staining (graded as 0, 1+, 2+ and 3+) by the percentage of the tumor cells showing staining, with the staining scores ranging from a minimum of 0 to a maximum score of 300. Staining score of 1 or more was considered positive.

Data was analyzed using the statistical software SPSS version 23. Chi-square analysis and Kruskall-Waalis test were performed to evaluate the correlation between GATA-3, GCDFP-15 and Mammaglobin expression. A p value of <0.001 was considered statistically significant.

The sensitivity and staining scores for GATA-3, GCDFP-15 and mammaglobin were compared in primary breast carcinomas, triple negative breast carcinomas and metastatic breast carcinomas (Figure 2).

Results

Hundred cases of primary breast carcinomas were included in the study. The age of the patients ranged from 29-93 years, with a mean age of 54 years. All the patients were females, except for two male patients. Primary breast carcinomas constituted 93 cases of Invasive ductal carcinoma, Not otherwise specified (IDC-NOS), four cases of Lobular carcinoma, two cases of Metaplastic carcinoma and one case of Mucinous carcinoma (Figure 3).

The IHC results of GATA-3, GCDFP-15 and mammaglobin are summarized in Table 2. Primary breast carcinomas which constituted total of 100 cases included triple negative breast carcinoma as well as non-triple negative breast carcinomas, that is the cases which expressed either ER or PR and/or amplification of Her2/neu. Amongst these 100 cases of primary breast carcinomas, 92 cases showed staining for GATA-3 with sensitivity being 92%. Mammaglobin showed a sensitivity of 68% (68/100 cases) and GCDFP-15 showed a sensitivity of 48% (48/100 cases). The sensitivity of GATA-3 expression was definitely more than mammaglobin and GCDFP-15 in primary breast carcinomas. A statistically significant difference was demonstrated between GATA-3 staining and staining of GCDFP-15 and mammaglobin ($p<0.001$ by Chi Square test).

Out of the 100 cases of primary breast carcinomas, 20 cases were of triple negative breast carcinomas. Amongst these 20 TNBC cases, GATA-3 showed a sensitivity of 60% (12/20 cases), mammaglobin showed a sensitivity of 25% (05/20 cases), while GCPDF-15 showed a sensitivity of 5% (01/20 cases). A p value of <0.001 was statistically significant between the staining of GATA-3 and staining of GCDFP-15 and mammaglobin ($p<0.001$ by Chi Square test).

30 cases of metastatic carcinomas were included in the study with metastasis to axillary lymph nodes in 25 cases, metastasis to cervical lymph nodes and supraclavicular lymph node in two cases each and one case of abdominal

Table 1. Details of Antibodies Used in Immunohistochemistry

Antibody	Clone	Source	Dilution	Antigen retrieval	Primary incubation	Instrument
GATA3	L50-823	Biocare	Prediluted, ready to use	Bond epitope retrieval solution, Tris EDTA based solution, pH 9 at 100^{O}C	45 min, 37^{O}C	Leica BondMax
Mammaglobin	304-1A5	Dako	Prediluted, ready to use	Bond epitope retrieval solution, Tris EDTA based solution, pH 9 at 100^{O}C	45 min, 37^{O}C	
GCDFP-15	23A3,	Dako	Prediluted, ready to use	Bond epitope retrieval solution, Tris EDTA based solution, pH 9 at 100^{O}C	45 min, 37^{O}C	Leica BondMax

GATA3, GATA3 binding protein; GCDFP-15, Gross cystic disease fluid protein 15

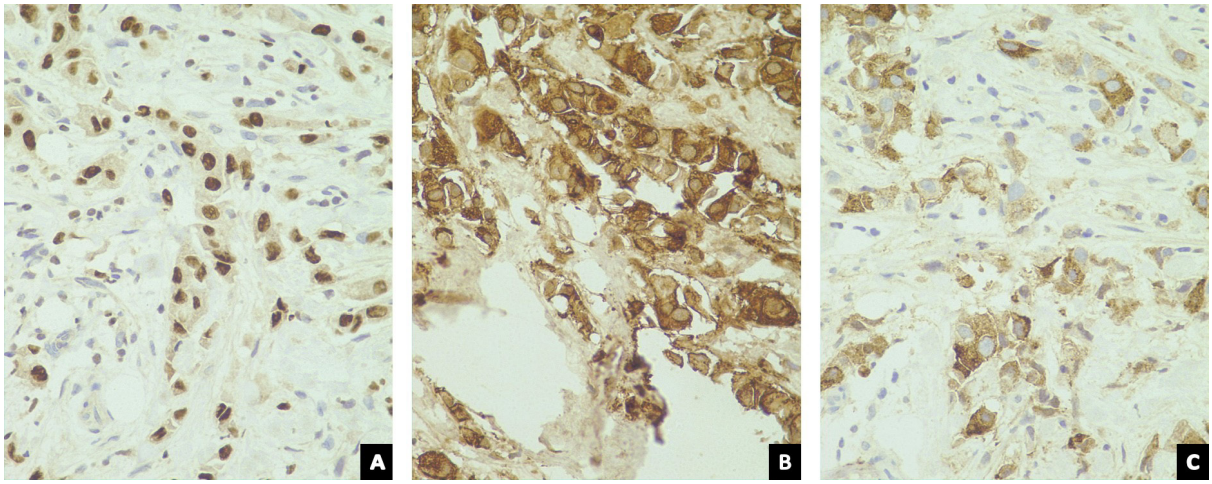

Figure 1. Staining Pattern. Nuclear positivity for GATA3 (A) and cytoplasmic staining for mammaglobin (B) and GCDFP-15 (C) (IHC, 400 ×)

Table 2. GATA3, Mammaglobin and GCDFP-15 Staining in Primary, Metastatic and Triple Negative Breast Carcinomas

	GATA3	Mammaglobin	GCDFP-15
Primary breast carcinomas	92/100 (92%)	68/100 (68%)	48/100 (48%)
Metastatic breast carcinomas	24/30 (80%)	17/30 (57%)	08/30 (27%)
Triple negative breast carcinomas	12/20 (60%)	05/20 (25%)	01/20 (5%)
Mean staining score	270	180	60

GATA3, GATA3 binding protein; GCDFP-15, Gross cystic disease fluid protein 15

deposits. In metastatic carcinomas, GATA-3 showed a positivity in 80% cases (24/30 cases), which was more than mammaglobin, which was positive in 56.6% cases (17/30 cases), and GCDFP-15 which was positive in 26.6% cases (08/30 cases). A statistically significant difference was demonstrated between GATA-3 staining and staining of GCDFP-15 and mammaglobin ($p<0.001$ by Chi Square test).

Staining score was calculated for each marker by multiplying the intensity of staining (graded as 0, 1+, 2+

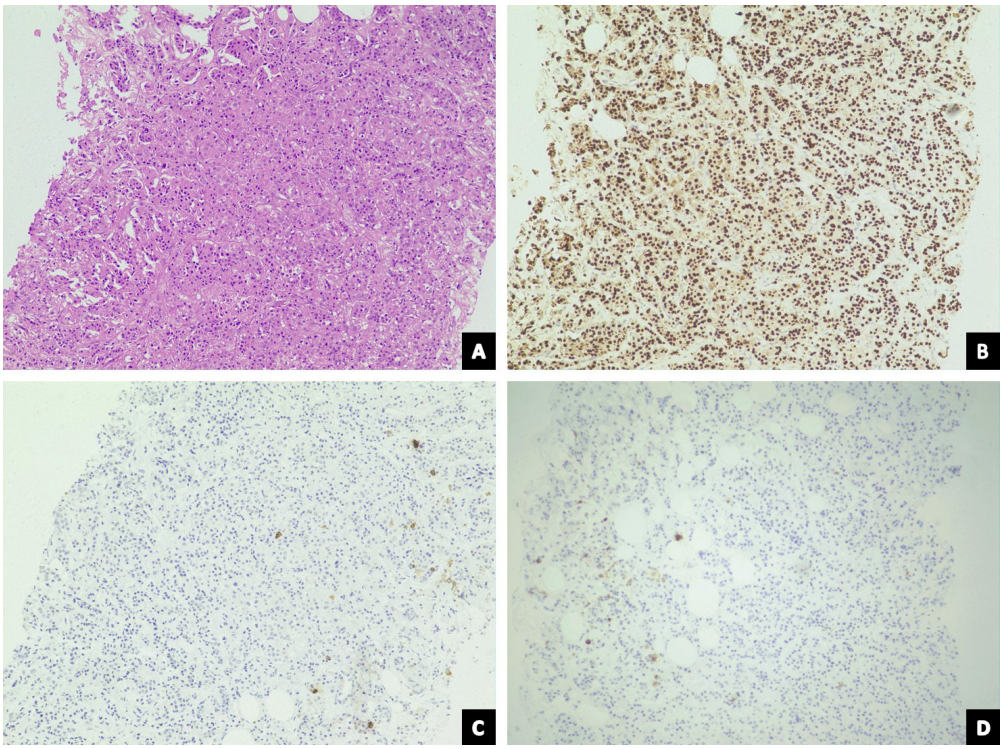

Figure 2. Primary Breast Carcinoma. H and E (100×) (A), Immunohistochemical staining for GATA-3 shows strong nuclear positivity (B), and focal positivity for Mammaglobin (C) and GCDFP-15 (D) (IHC, 100 ×).

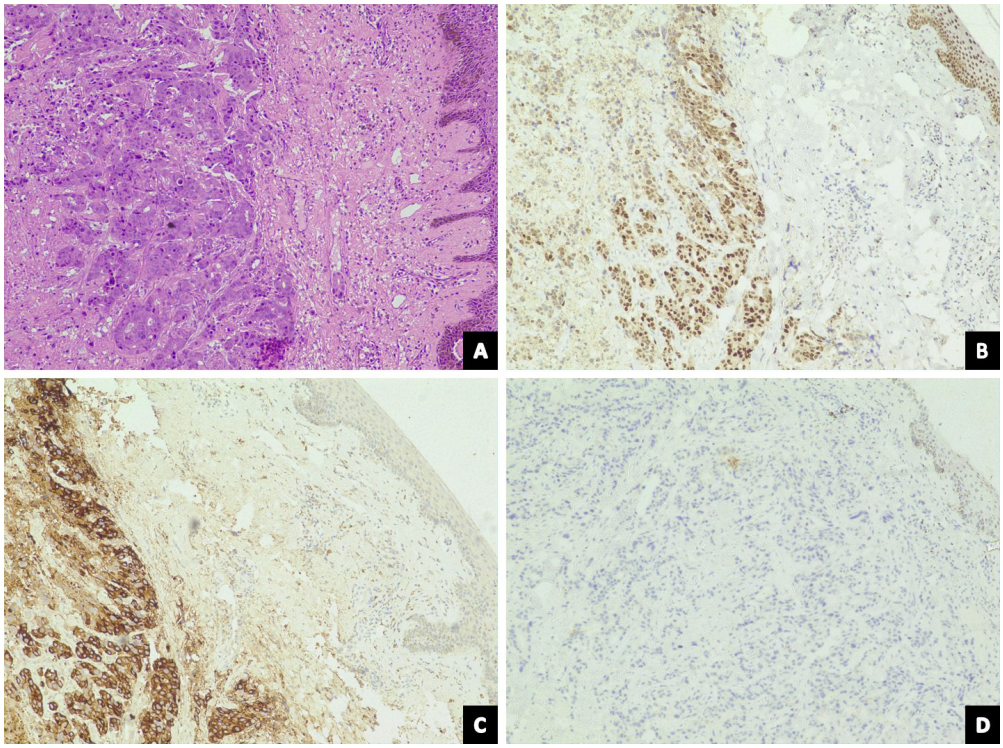

Figure 3. Invasive Ductal Carcinoma. H and E (100 ×) (A), Immunohistochemical staining for GATA-3 shows nuclear positivity (B), strong cytoplasmic positivity for Mammaglobin (C) and immune-negative for GCDFP-15 (D) (IHC, 100 ×).

Table 3. Distribution of Staining Score for GATA3, Mammaglobin and GCDFP-15 in Total 130 Cases (Primary Breast Carcinomas: 100 cases, including 20 triple negative cases and 30 cases of metastatic breast carcinomas)

Staining score	GATA3	Mammaglobin	GCDFP-15
5-50	0/130 (0%)	05/130 (3.8%)	29/130 (22.3%)
51-100	0/130 (0%)	15/130 (11.5%)	21/130 (16.15%)
101-200	42/130 (32.3%)	31/130 (23.8%)	05/130 (3.8%)
201-300	74/130 (56.92%)	34/130 (26.15%)	01/130 (0.76%)

GATA3, GATA3 binding protein; GCDFP-15, Gross cystic disease fluid protein 15

and 3+) by the percentage of the tumor cells showing staining. Staining score was categorized in four groups as 5-50, 51-100, 101-200 and 201-300. The staining score of GATA-3 ranged from 140 to 300, with an average score of 270. The staining score of mammaglobin ranged from 5 to 300, with an average score of 180 and the staining score of GCDFP-15 ranged from 2 to 300, with an average score of 60. The staining score distribution is depicted in Table 3. GATA-3 demonstrated to have higher staining score (201-300) than other two markers in maximum number of cases (74/130 cases) (Table 3). A p-value of <0.001 was noted between the staining score of the three markers which was statistically significant (Kruskaal-Waalis Test).

Table 4: GATA-3, Mammaglobin and GCDFP-15 Expression in Primary Breast Carcinomas, Triple Negative Breast Carcinomas and Metastatic Breast Carcinomas

Positive markers	Primary (n=100)	TNBC (n=20)	Metastatic (n=30)
All three	38 (38%)	1 (5%)	4 (13.3%)
GATA-3, Mammaglobin	27 (27%)	3 (15%)	12 (40%)
GATA-3, GCDFP-15	10 (10%)	0 (0%)	3 (10%)
Mammaglobin, GCDFP-15	0 (0%)	0 (0%)	1 (3.3%)
GATA-3	17 (17%)	9 (45%)	5 (16.6%)
Mammaglobin	2 (2%)	1 (5%)	0 (0%)
GCDFP-15	0 (0%)	0 (0%)	0 (0%)
None	6 (6%)	6 (30%)	5 (16.6%)

GATA3, GATA3 binding protein; GCDFP-15, Gross cystic disease fluid protein 15

Out of the 100 cases of primary breast carcinoma, 38 cases demonstrated immunoreactivity with all three markers GATA-3, Mammaglobin and GCDFP-15; whereas six cases were negative for all three markers. GATA-3 staining was found to be superior to other two markers. GATA-3 was positive in 27 cases where Mammaglobin was negative, in 44 cases were GCDFP-15 was negative and in 17 cases where both Mammaglobin and GCDFP-15 was negative. Mammaglobin was positive in two cases where GATA-3 was negative and GCDFP-15 was not positive in any GATA-3 negative case (Table 4).

Amongst 30 metastatic carcinoma cases, all three markers were positive in four cases and negative in five cases. GATA-3 was positive in eight Mammaglobin-negative cases and in 17 GCDFP-15 negative cases. Only one GATA-3 negative case demonstrated positivity for both Mammaglobin and GCDFP-15. Similarly, in TNBCs, one case was immunoreactive for all three markers and six cases were negative for all three markers. GATA-3 was positive in nine cases where other two markers were negative.

Discussion

The primary objective of this study was to evaluate the performance of GATA-3, Mammaglobin and GCDFP-15 immunohistochemistry in primary breast carcinoma, including triple negative breasts carcinomas, and metastatic breast carcinomas, in respect to the staining score which indicated both quantitative (percentage of positive cells) and qualitative (intensity of staining) parameter. In addition to this, comparison between the three markers was done to examine the sensitivity of the marker.

GCDFP-15 has been used as a marker of primary breast carcinoma since 1980s, with sensitivity ranging from 23% to 73% (Gown et al., 2016; Kandalaft et al., 2016). Other than breast, only a few tumors like prostate cancer, carcinoma of sweat gland and salivary gland are known to express GCDFP-15 (Darb-Esfahani et al., 2014; Huo et al., 2013). After a decade, Mammaglobin was identified as a novel marker which had sensitivity similar to that of GCDFP-15 (Kandalaft et al., 2016). Mammaglobin immunoreactivity has been observed in some other tumors including endometrial carcinoma, carcinoma of sweat gland, salivary gland, stomach, colon and ovary (Huo et al., 2013).

GATA-3 is regulator of luminal cell differentiation in mammary gland. Kouros-Mehr et al., (2008) demonstrated the presence of GATA-3 in luminal cells of mature ducts of pubertal and adult mice and its absence in the myoepithelial cells. They also stated that deletion of GATA-3 leads to loss of luminal differentiation, whereas its introduction induces luminal cell differentiation (Kouros-Mehr et al., 2008; McCleskey et al., n.d.). The association between GATA-3 and ER has been established previously (Clark et al., 2017; Voduc et al., 2008). Recent studies have demonstrated that GATA-3 is a more sensitive marker for mammary epithelial origin (Wendroth et al., 2015). It is known to have a higher expression in breast and urothelial carcinomas. Despite its lack of specificity due to expression in other tumors like squamous cell carcinoma, skin adnexal tumors, salivary gland neoplasm etc., it is still considered as a sensitive marker for breast carcinoma (Ni et al., 2018). Very few studies in the literature have reported the expression of GATA-3 in breast carcinomas in Indian population (Banik and Pal, 2022; Singh et al., 2021). GATA-3 expression in the current study had sensitivity of 92% in primary breast carcinomas, which significantly surpassed the sensitivity of already well-established breast-specific markers GCDFP-15 (48%) and Mammaglobin (68%). These results were similar to various studies in the literature which documented GATA-3 sensitivities between 88.8% to 96% (Clark et al., 2014; Deftereos et al., 2015; Kandalaft et al., 2016; Wendroth et al., 2015). A large study of 993 cases reported a GATA-3 sensitivity of 82.5% (Ni et al., 2018). The variable result can be corroborated to the difference in sample size. The choice of antibody (HG3-31 or L50-823) and different scoring systems can also lead to variable results (Hafez and Shaaban, 2018).

GATA-3 expression has been correlated with the hormone receptor status of breast carcinomas (Braxton et al., 2015; Voduc et al., 2008). Metastasis from triple negative breast carcinoma pose a diagnostic difficulty due to lack of expression of breast specific markers. Many studies have been published previously reporting the expression of GATA-3 and its comparison with mammaglobin and GCDFP-15 expression in triple negative breast carcinomas (Deftereos et al., 2015; Huo et al., 2015; Kandalaft et al., 2016; Krings et al., 2014; Ni et al., 2018). These studies reported the sensitivity for GATA-3, mammaglobin and GCDFP-15 in the range of 38.1% to 87 %, 7.1% to 31.7% and 10 to 22.3% respectively. We reported a sensitivity of 60% for GATA-3 which was significantly higher than the sensitivity of Mammaglobin and GCDFP-15 which were 25% and 5% respectively, which were similar to many studies (Deftereos et al., 2015; Krings et al., 2014). Ni et al., (2018) demonstrated the GATA-3 expression in TNBCs to be slightly lower which could be due to the difference in sample size of the study. Limited utility of mammaglobin and GCDFP-15 due to lack of sensitivity in TNBCs have been documented by some studies (Huo et al., 2013; Rakhshani and Daryakar, 2014).

The GATA-3 immunoreactivity in cytology specimens of metastatic breast carcinoma including both fine needle aspiration samples and serous effusion samples have been evaluated in the past (Braxton et al., 2015; El Hag et al., 2017; Hafez and Shaaban, 2018; Shield et al., 2014). These studies showed GATA-3 immunopositivity in the range 82.7% to 90 %. Similar to primary breast carcinoma, the current study also noted a higher expression of GATA-3 (80%) in metastatic breast carcinomas. These results were in concordance with numerous of studies in literature (Braxton et al., 2015; Deftereos et al., 2015; El Hag et al., 2017; Hafez and Shaaban, 2018; Ni et al., 2018; Sangoi et al., 2016; Shield et al., 2014). With a superior rate of expression of GATA-3 in metastatic breast carcinomas, this marker can definitely prove valuable in evaluating primary of unknown origin where breast is suspected to be the primary site. GATA3 can also be used to identify

a breast origin in a tumour expressing CK7+/CK20− and hormone receptors (Selves et al., 2018).

We also evaluated the combined sensitivity of two markers for diagnosing primary and metastatic breast carcinomas. It was noted that a combination of GATA-3/mammaglobin is far more sensitive than GATA-3/GCDFP-15 and mammaglobin/GCDFP-15 combination. Adding mammaglobin to GATA-3 has been shown to improve the sensitivity (Hafez and Shaaban, 2018; Shield et al., 2014).

In addition to lower sensitivity of GCDFP-15 and mammaglobin, 'equivocal' staining results (weak and/or focal staining) with background staining can lead to diagnostic difficulty (Bhargava et al., 2007; Sangoi et al., 2016). GATA-3 is a nuclear stain and shows less background staining, making it qualitatively superior to other two markers. Less background staining was particularly beneficial in mucinous carcinomas where mucin was not stained by GATA-3 as opposed to other two markers (Deftereos et al., 2015). The higher sensitivity and staining pattern of GATA-3 without any background staining also proves to be beneficial in cases where tissue is scant. Evaluating the immunoreactivity of nuclear markers like GATA-3 is much more reliable than the cytoplasmic positivity of mammaglobin and GCDFP-15 on scant tissue samples (Sangoi et al., 2016).

The current study used L50-823 clone of GATA-3 for staining. Other studies in literature have documented the use of two clones of GATA-3. Most of the studies used L50-823 clone, while few used HG3-31 clone (Braxton et al., 2015; Cimino-Mathews et al., 2013; Deftereos et al., 2015; El Hag et al., 2017; Hafez and Shaaban, 2018; Huo et al., 2015; Miettinen et al., 2014; Sangoi et al., 2016; Shield et al., 2014; Voduc et al., 2008). Two studies evaluated and compared both the clones. Kandalaft et al., (2016) demonstrated a sensitivity of 96% for both clones in primary breast carcinomas overall; and a sensitivity of 87% and 63% for L50-823 and HG3-31 clone respectively in TNBCs. Another study documented sensitivity of 66% and 44% for L50-823 and HG3-31 clone respectively in TNBCs (Krings et al., 2014). Results from these studies show that L50-823 is a more sensitive clone for triple negative breast carcinoma.

In conclusion, GATA-3 showed a better expression than GCDFP-15 and Mammaglobin in primary breast carcinomas as well as metastatic breast carcinomas. Moreover, GATA-3 has a nuclear expression which helps in better interpretation. Mammaglobin is shown to have a slightly lower sensitivity than GATA-3 and can show background staining posing a difficulty in interpretation (Clark et al., 2014). GCDFP-15 is even a less sensitive marker for breast carcinomas. The only drawback of GATA-3 immunomarker can be its lack of specificity as it can be expressed in tumors from other sites (Clark et al., 2014; Miettinen et al., 2014). The limitation of this study can be attributed to moderate sample size. However, our results are similar to previous studies conducted.

Thus, GATA-3 proves to be a useful and sensitive immunomarker for breast carcinomas when compared to other traditionally established markers (Mammaglobin and GCDFP-15). It can specially be useful in metastatic breast carcinoma when considered in panel with other immunohistochemical markers.

Author Contribution Statement

Conceptualization: MR; Data curation: MR, SK, RS, PS, GY; Formal analysis: MR, SK, RKC, PS, GY, PAE; Funding acquisition: MR; Investigation: MR, SK; Methodology: MR, SK, AN; Project administration: MR, SK; Software: MR, AG; Writing – original draft: MR, SK; Writing – review and editing: MR, AN; Approval of final manuscript: all authors

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Ethical Declaration

This study was ethically reviewed and approved by the institutional board ethics committee of All India Institute of Medical Sciences, Jodhpur (Certificate number: AIIMS/IEC/2017/750).

Conflict of Interests

The authors declare that they have no conflict of interest.

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