The Egyptian Journal of Hospital Medicine (April 2025) Vol. 99, Page 1692-1704

# The significance of the Ferroptosis Markers (SLC7A11, ACSL4) and Their Relation to M6A Modification Regulators (HNRNPA2B1, YTHDF1) in Breast Invasive Ductal Carcinoma

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## ABSTRACT

**Background:** Ferroptosis which is a unique type of regulated cell death, has been featured as an urgent mechanism in development and progression of cancer, especially regarding the resistance to chemotherapy.

**Subjects and methods:** This retrospective study involved immunohistochemical analysis of SLC7A11, ACSL4, HNRNPA2B1, and YTHDF1 expression in 95 cases of invasive ductal carcinoma of the breast, all had been treated with neoadjuvant chemotherapy.

**Results:** Positive expression of SLC7A11 was identified in 63.2% of cases and demonstrated a statistically significant linear association with tumor grade, clinical tumor stage, clinical lymph node (LN) stage, postoperative pathological tumor and nodal staging and molecular subtypes. High expression of ACSL4 was observed in 51.6% of cases and demonstrated a statistically significant inverse relationship with tumor grade, clinical tumor staging, clinical lymph node (LN) staging, and postoperative pathological tumor and nodal staging. Positive HNRNPA2B1 expression was apparent in 64.2% of cases and exhibited a statistically significant relationship with tumor grade, clinical tumor staging, clinical LN staging, pathological tumor and nodal staging (postoperative) and molecular type. High expression of YTHDF1 was apparent in 62.1% of cases and exhibited statistically significant relationship with tumor grade, clinical tumor staging, clinical LN staging, pathological tumor and nodal staging. Pathological complete response (pCR) was significantly frequent in cases with early clinical tumor and nodal stage, negative SLC7A11 expression (ferroptosis inhibitor), high ACSL4 level (ferroptosis inducer), negative HNRNPA2B1 and low YTHDF1 expression.

**Conclusion:** The expression of ferroptosis regulators SLC7A11 and ACSL4 significantly impacted the therapeutic response to neoadjuvant chemotherapy suggesting their value as predictive markers and promising therapeutic targets for breast ductal carcinoma. Furthermore, the m6A modifications of ferroptosis regulators SLC7A11 and ACSL4, mediated by HNRNPA2B1 and YTHDF1, may serve as a mechanism for inducing ferroptosis in breast cancer.

**Keywords:** SLC7A11, ACSL4, HNRNPA2B1, YTHDF1, Ferroptosis, Breast invasive ductal carcinoma.

## INTRODUCTION

Breast cancer is the most prevalent cancer and the leading cause of cancer-related mortality in women worldwide. Breast cancer is well known to be a heterogeneous disease that exhibits significant diversity in molecular subtypes, histological features, and prognostic outcomes in addition to variable responses to conventional therapy. Chemotherapy resistance is one of the most challenging problems in the treatment of breast cancer. Accumulating evidence supports ferroptosis as a potential target for chemotherapy resistance. Recent research highlights ferroptosis as a promising therapeutic target to overcome chemotherapy resistance [(1)].

Ferroptosis represents a non-apoptotic, unique type of programmed cell death. It is defined by the accumulation of lipid peroxides to toxic levels, which is dependent on iron. The process is typically triggered by iron-dependent oxidative stress. The central mechanistic pathway of ferroptosis involves the iron-mediated peroxidation of polyunsaturated fatty acids (PUFAs) embedded within the cellular membrane [(2)]. The lipid peroxidation is catalyzed by divalent iron ions and enzymes such as lipoxygenases, ultimately leading to the disruption of cellular integrity and triggering cell death. Ferroptosis holds potential as a novel therapeutic target in oncology, particularly in cancers exhibiting resistance to conventional chemotherapy treatments [(3)]. SLC7A11 (Solute Carrier Family 7 Member 11) represents a vital transporter that enables the exchange of extracellular cysteine for intracellular glutamate. The cysteine is then converted to cysteine that serves as a precursor in the synthesis of glutathione, a compound essential for reducing oxidative stress and promoting cellular survival in challenging conditions. This metabolic regulation is essential for cellular growth and proliferation [(4)]. SLC7A11 is ubiquitously expressed across various modulating critical cellular processes such as redox homeostasis, metabolic adaptation and ferroptosis [(5)]. ACSL4 (acyl-CoA synthetase long chain family member 4) has been implicated in ferroptosis acting as a positive regulator. Through its catalytic action on long-chain fatty acids, ACSL4 facilitates the generation of lipid peroxides, a hallmark of ferroptotic cell death, highlighting its central role in the regulation of oxidative stress-induced cellular damage [(6)].

N6-methyladenosine (m6A) constitutes one of the most prevalent and well-characterized RNA modifications, playing a critical role in various aspects of messenger RNA (mRNA) regulation. Recent studies have highlighted that m6A and its regulatory modulators comprising writers, readers and erasers have multifaceted role in carcinogenesis, tumor advancement, and the emergence of resistance to conventional therapies in multiple cancers [(7)]. However, the precise molecular pathways linking m6A modification and ferroptosis in cancer remain largely unexplored and require further investigation.



Received: 29/12/2024
Accepted: 29/02/2025

Heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1), is a well-characterized m6-methyladenosine (m6A) reader protein. Functionally, it exerts regulatory control over post-transcriptional gene expression by selectively binding to RNA motifs in a sequence-dependent manner. Accumulating evidence implicates HNRNPA2B1 as a pivotal modulator of oncogenic phenotypes, facilitating neoplastic cell motility and invasiveness through its influence on metabolic reprogramming pathways [(8)]. Consequently, delineating the oncogenic contributions of HNRNPA2B1 in the context of breast carcinoma represents a critical pre-requisite for prognostic and a therapeutic target.

YTH N6-methyladenosine RNA binding protein 1 (YTHDF1), a prominent member of the YTH domain-containing protein family, functions as an m6A "reader," mediating the translation of m6A-modified messenger RNAs (mRNAs) within the cytoplasmic compartment. Many studies demonstrated that YTHDF1 is aberrantly upregulated in a variety of malignancies, with its expression levels correlating with adverse clinical outcomes and poor prognostic indicators [(9)]. However; the precise mechanisms by which YTHDF1 contributes to breast cancer remain unclear. Recent studies suggest the idea that induction of ferroptosis may be explored as a promising therapeutic strategy in malignant tumors. Building upon this, the current study was designed to investigate the immunohistochemical expression of key ferroptosis-related markers (SLC7A11, ACSL4) in invasive ductal carcinoma of the breast and to assess their relation to M6A modification regulators (HNRNPA2B1, YTHDF1) besides evaluation of their probable potential impact on response to neoadjuvant chemotherapy and progression of the disease.

## MATERIAL AND METHODS

**Subjects:** This retrospective study involved core biopsy of 95 cases of invasive ductal carcinoma of the breast (NOS). All patients included in this study received neoadjuvant chemotherapy (6 cycles) prior to surgical intervention of the tumor. The study utilized archival formalin-fixed, paraffin-embedded tissue blocks of core biopsy of breast carcinoma cases obtained from the Pathology Department and Early Cancer Detection Unit at Benha University's Faculty of Medicine, and processed between 2021 and 2023. Extraction of clinico-pathological data including patient' age, tumor size, tumor grade and molecular subtyping was done through examination of pathology reports and medical clinical records of Oncology Unit.

Clinical tumor stage and clinical lymph node (LN) staging before the neoadjuvant therapy were recognized according to radiological and clinical assessment. After post-neoadjuvant surgery, both pathological tumor staging and nodal staging were assessed according to yAJCC system. Response to neoadjuvant chemotherapy (NAC) was extracted from files and revised. Response to NAC was detected according to pathological examination after surgery whether lumpectomy or mastectomy with axillary clearance. The spectrum of response to neoadjuvant chemotherapy varies from pathological complete response (pCR), partial response, and no response.

**Exclusion criteria:** Patients with metastatic disease (M1).

**Histopathological analysis:** Formalin-fixed, paraffin-embedded tissue sections, each 4 micrometers in thickness, were stained by conventional Hematoxylin and Eosin (H & E). All histological slides were independently evaluated by two experienced pathologists. The evaluation included:

1. **Verification of diagnosis:** Confirmation of the initial histopathological diagnosis in accordance with the 2022 World Health Organization (WHO) classification of breast tumors.
2. **Tumor grading:** Determination of histological grade using the Elston-Ellis modification of the Bloom-Richardson grading system (Also, referred to as the Nottingham grading system).
3. **Tumor staging:** Pathological staging of the neoplasm was performed based on the Tumor-Node-Metastasis (TNM) criteria, as outlined by the American Joint Committee on Cancer (AJCC).

**Immunohistochemical study:** Immunohistochemical (IHC) staining was performed on 4-micrometer thick sections of formalin-fixed, paraffin-embedded tissue samples. The sections were processed and immunostained using primary antibodies according to the manufacturer's protocols. Detailed data of antibodies was summarized in table (1). The positive controls used for each immunohistochemical primary antibody are described in table (1).

**Table (1):** The data of the used primary antibodies

| Antibody | Company | Clone | Positive control | Staining pattern |
|---|---|---|---|---|
| **SLC7A11** | Thermo Fisher Scientific | (A7C6-R) Rabbit Monoclonal Antibody | Lung adenocarcinoma | Cytoplasmic |
| **ACSL4** | | (HL229) Rabbit Monoclonal Antibody | Hepatocellular Carcinoma | Cytoplasmic |
| **HNRNPA2B1** | | (3H6F7) Rabbit Monoclonal Antibody | Glioblastoma | Nuclear |
| **YTHDF1** | | (PSH0-23) Rabbit Monoclonal Antibody | Lung cancer | Cytoplasmic |

**Immunohistochemical assessment: SLC7A11**:

The expression was cytoplasmic. The intensity was graded as follow: 0 (no staining), 1 (weak), 2 (moderate) and 3 (strong). The percent of stained cells was also evaluated as: 0 = 0% / 1 = 1–25% / 2 = 26–50% / 3 = 51–75% and 4 = 76–100%. The final score was calculated by multiplying the intensity by the extent, yielding a total IHC score ranging from 0 to 12. The IHC score between 0 and 3 was considered indicative of negative staining, while a score ranging from 4 to 12 was classified as positive staining [(10)].

1. **ACSL4:** The expression was localized to the cytoplasm. The staining intensity was graded as follow: 1 (weak), 2 (moderate), 3 (strong), and 4 (very strong). The percent of positive cells was scored as follows: 1 = 0 – 25%, 2 = 26–50%, 3 = 51–75% and 4 >75%. Multiplication of the intensity score by the percent of positive cells was applied for final score. An overall score of 8 or greater (≥ 8) was categorized as high expression, while scores below 8 were considered indicative of low expression [(11)].
2. **HNRNPA2B1:** The expression was observed in the nucleus. The proportion of positively stained cells was as follows: 1≤ 25%, 2: 26%–50%, 3: 51%–75%, and 4: 76%–100%. The intensity of staining was as follow: 0 (none), 1 (weak), 2 (moderate), and 3 (strong). Multiplication of the intensity score by the percent of positive cells was applied for final score. A total expression score of ≥5 was classified as positive expression [(12)].
3. **YTHDF1:** YTHDF1 expression was detected in the cytoplasm. The intensity of staining was evaluated as follows: 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). The percent of stained cells was as follow: 0 (0%), 1: 1–25%, 2: 26–50%, 3: 51–75% and 4:76–100%. Multiplication of the intensity score by the percent of positive cells was applied for final score. Overall score more than 6 (≥ 6) was defined as high expression, whereas the other scores less than 6 represented low expression [(13)].

**Ethical approval: Approval by The Ethical Committee, Faculty of Medicine, Benha University (Code Number: RC 16-11-2024) was obtained. Following receipt of all information, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.**

***Statistical analysis***

Statistical analysis was performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the Chi-square ($\chi^2$) test or Fisher's exact test, as appropriate. Associations between non-parametric variables were assessed by Spearman's rank correlation coefficient (ρ). A p-value ≤ 0.05 was considered indicative of statistical significance.

## RESULTS

**Clinicopathological results:** The present retrospective study was carried out on a cohort of 95 Egyptian cases diagnosed as invasive ductal carcinoma (NOS) of the breast. All patients received Neoadjuvant chemotherapy prior to surgical intervention. The summary of the clinicopathological data was presented in table (2).

**Table (2):** Clinicopathological parameters of breast invasive ductal carcinoma (NOS) study cases

| Clinicopathological variables | | Number | Percent |
|---|---|---|---|
| **Age (Years)** | **Mean ± SD (range)** | | |
| **Age Group** | **< 50** | **40** | **42.1%** |
| | **≥ 50** | **55** | **57.9%** |
| **Tumor Grade** | **Grade I** | **8** | **8.4%** |
| | **Grade II** | **46** | **48.4%** |
| | **Grade III** | **41** | **43.2%** |
| **Clinical Tumor Staging (Before Neoadjuvant Therapy)** | **T1** | **11** | **11.6%** |
| | **T2** | **38** | **40.0%** |
| | **T3** | **36** | **37.9%** |
| | **T4** | **10** | **10.5%** |
| **Clinical LN Staging (Before Neoadjuvant therapy** | **N 0** | **8** | **8.4%** |
| | **N1/ N2/ N3** | **87** | **91.6%** |
| **Pathological Tumor Staging (Post-Operative)** | **ypT0** | **27** | **28.4%** |
| | **ypT1** | **28** | **29.5%** |
| | **ypT2** | **15** | **15.8%** |
| | **ypT3** | **19** | **20.0%** |
| | **ypT4** | **6** | **6.3%** |
| **Pathological LN Staging (Post-Operative)** | **ypN0** | **27** | **28.4%** |
| | **ypN1/ ypN2/ ypN3** | **68** | **71.6%** |

| Clinicopathological variables | | Number | Percent |
|---|---|---|---|
| Molecular subtypes | Luminal A | 36 | 37.9% |
| | Luminal B | 22 | 23.2% |
| | HER2-enriched | 17 | 17.9% |
| | Triple-negative | 20 | 21.1% |
| Response to Neoadjuvant chemotherapy | No response | 28 | 29.5% |
| | Partial response | 42 | 44.2% |
| | pCR | 25 | 26.3% |
| Total | | 95 | 100% |

**Immunohistochemical results:**

**SLC7A11 Immunohistochemical results:** The expression of SLC7A11 was primarily observed in the cytoplasm. Positive SLC7A11 expression was identified in 60 out of 95 (63.2%) cases of breast ductal carcinoma. A statistically significant linear association was found between positive SLC7A11 expression and clinicopathological parameters, including clinical staging (tumor and nodal: $P < 0.001$/ $P < 0.05$), post-operative pathological stage (tumor and nodal: $P < 0.001$ each), tumor grade ($P < 0.05$), and molecular subtypes ($P < 0.05$). Pathological complete response (pCR) was significantly associated with negative SLC7A11 expression ($P < 0.001$) suggesting a potential relationship with ferroptosis. This was detailed in table (3).

**Table (3):** Relation of SLC7A11 with clinicopathological parameters of study cases

| Clinicopathological variables | | | SLC7A11 | | Test of Significance |
|---|---|---|---|---|---|
| | | | Negative | Positive | |
| Age Group | < 50 | 40 | 11(27.5%) | 29(72.5%) | P = .110 |
| | ≥ 50 | 55 | 24(43.6%) | 31(56.4%) | |
| Tumor Grade | I | 8 | 5(62.5%) | 3(37.5%) | P < 0.05* |
| | II | 46 | 19(41.3%) | 27(58.7) | |
| | III | 41 | 11(25.8%) | 30(73.2%) | |
| Clinical Tumor Staging (Before neoadjuvant Therapy) | T1 | 11 | 7(63.6%) | 4(36.4%) | P < 0.001** |
| | T2 | 38 | 18(47.4%) | 20(52.6%) | |
| | T3 | 36 | 8(22.2%) | 28(77.8%) | |
| | T4 | 10 | 2(20%) | 8(80%) | |
| Clinical LN Staging (Before neoadjuvant therapy | N 0 | 8 | 6 (75.0%) | 2(25.0%) | P < 0.05* |
| | N 1/ N2/ N3 | 87 | 29(33.3%) | 58(66.7%) | |
| Pathological Tumor Staging (Post-Operative) | ypT0 | 27 | 19(70.4%) | 8(29.6%) | P < 0.001** |
| | ypT1 | 28 | 12(42.8%) | 16(57.25) | |
| | ypT2 | 15 | 2(13.3%) | 13(86.7%) | |
| | ypT3 | 19 | 2(10.5%) | 17(89.5%) | |
| | ypT4 | 6 | 0(0%) | 6(100%) | |
| Pathological LN Staging (Post-Operative) | ypN0 | 27 | 18(66.7%) | 9(33.3%) | P < 0.001** |
| | ypN1/ ypN2/ ypN3 | 68 | 17(25.0%) | 51(75.0%) | |
| Molecular subtypes | Luminal A | 36 | 19(52.8%) | 17(47.2%) | P < 0.05* |
| | Luminal B | 22 | 7(31.8%) | 15(68.2%) | |
| | HER2-enriched | 17 | 5(29.4%) | 12(70.6%) | |
| | Triple-negative | 20 | 4(20.0%) | 16(80.0%) | |
| Response to neoadjuvant chemotherapy | No response | 28 | 5(17.9%) | 23(82.1%) | P < 0.001** |
| | Partial response | 42 | 14(33.3%) | 28(66.7%) | |
| | pCR | 25 | 16(64.0%) | 9(36.0%) | |
| Total | | 95 | 35 (36.8%) | 60 (63.2%) | |

**ACSL4 immunohistochemical results:** The expression was localized to the cytoplasm. High ACSL4 expression was detected in 49 out of 95 (51.6%) cases of breast ductal carcinoma. High ACSL4 expression exhibited a statistically significant inverse association with clinical staging (tumor and nodal: P < 0.001 each) and postoperative pathological staging (tumor and nodal: P < 0.001 each) and tumor grade (P<0.001). The pathological complete response (pCR) was significantly associated with elevated ACSL4 expression (P < 0.001), suggesting potential link to ferroptosis. This was detailed in table (4).

**Table (4):** Relation of ACSL4 with clinicopathological parameters of study cases

| Clinicopathological variables | | | ACSL4 | | Test of Significance |
|---|---|---|---|---|---|
| | | | Low | High | |
| Age Group | < 50 | 40 | 19(47.5%) | 21(52.5%) | P= .880 |
| | ≥ 50 | 55 | 27(49.1%) | 28(50.9%) | |
| Tumor Grade | I | 8 | 2(25.0%) | 6(75.0%) | P < 0.001** |
| | II | 46 | 17(37.0%) | 29(63.0%) | |
| | III | 41 | 27(65.9%) | 14(34.1%) | |
| Clinical Tumor Staging (Before neoadjuvant Therapy) | T1 | 11 | 3(27.3%) | 8(72.7%) | P < 0.001** |
| | T2 | 38 | 10(26.3%) | 28(73.7) | |
| | T3 | 36 | 24(66.7%) | 12(33.3%) | |
| | T4 | 10 | 9(90%) | 1(10%) | |
| Clinical LN Staging (Before neoadjuvant therapy | N 0 | 8 | 0(0%) | 8(100%) | P < 0.001** |
| | N 1/ N2/ N3 | 87 | 46(52.9%) | 41(47.1%) | |
| Pathological Tumor Staging (Post-Operative) | ypT0 | 27 | 7(25.9%) | 20(74.1%) | P < 0.001** |
| | ypT1 | 28 | 11(39.3%) | 17(60.7%) | |
| | ypT2 | 15 | 6(40.0%) | 9(60.0%) | |
| | ypT3 | 19 | 16(84.2%) | 3(15.8%) | |
| | ypT4 | 6 | 6(100%) | 0(0%) | |
| Pathological LN Staging (Post-Operative) | ypN0 | 27 | 5(18.5%) | 22(81.5%) | P < 0.001** |
| | ypN1/ ypN2/ ypN3 | 68 | 41(60.3%) | 27(39.7%) | |
| Molecular subtypes | Luminal A | 36 | 13(36.1%) | 23(63.9%) | P = .057 |
| | Luminal B | 22 | 12(54.5%) | 10(45.5%) | |
| | HER2-enriched | 17 | 8(47.1%) | 9(52.9%) | |
| | Triple-negative | 20 | 13(65.0%) | 7(35.0%) | |
| Response to neoadjuvant chemotherapy | No response | 28 | 22(78.6%) | 6(21.4%) | P < 0.001** |
| | Partial response | 42 | 19(45.2%) | 23(54.8%) | |
| | pCR | 25 | 5(20.0%) | 20(80.0%) | |
| Total | | 95 | 46 (48.4%) | 49 (51.6%) | |

**HNRNPA2B1 immunohistochemical results:** The expression was localized to the nucleus. Positive HNRNPA2B1 expression was observed in 61 out of 95 (64.2%) cases of breast ductal carcinoma. A statistically significant linear relation was found between positive HNRNPA2B1 expression and clinical staging (tumor and nodal: $P < 0.001$ each), postoperative pathological staging (tumor and nodal: $P < 0.05$/ $P < 0.001$), tumor grade ($P < 0.001$), and molecular subtypes ($P < 0.05$). The pathological complete response (pCR) was significantly associated with negative HNRNPA2B1 expression ($P < 0.001$). This was detailed in table (5).

**Table (5):** Relation of HNRNPA2B1 with clinicopathological parameters of study cases

| Clinicopathological variables | | | HNRNPA2B1 | | Test of Significance |
|---|---|---|---|---|---|
| | | | Negative | Positive | |
| Age Group | < 50 | 40 | 12(30.0%) | 28(70.0%) | P= .321 |
| | ≥ 50 | 55 | 22(40.0%) | 33(60.0%) | |
| Tumor Grade | I | 8 | 5(62.5%) | 3(37.5%) | P < 0.001** |
| | II | 46 | 20(43.5%) | 26(56.5%) | |
| | III | 41 | 9(22.0%) | 32(78.0%) | |
| Clinical Tumor Staging (Before neoadjuvant Therapy) | T1 | 11 | 8(72.7%) | 3(27.3%) | P < 0.001** |
| | T2 | 38 | 21(55.3%) | 17(44.7%) | |
| | T3 | 36 | 4(11.1%) | 32(88.9%) | |
| | T4 | 10 | 1(10%) | 9(90%) | |
| Clinical LN Staging (Before neoadjuvant therapy | N 0 | 8 | 6(75.0%) | 2(25.0%) | P < 0.001** |
| | N 1/ N2/ N3 | 87 | 28(32.2%) | 59(67.8%) | |
| Pathological Tumor Staging (Post-Operative) | ypT0 | 27 | 19(70.4%) | 8(29.7%) | P < 0.05* |
| | ypT1 | 28 | 11(39.3%) | 17(60.7%) | |
| | ypT2 | 15 | 2(13.3%) | 13(86.7%) | |
| | ypT3 | 19 | 1(5.3%) | 18(84.7%) | |
| | ypT4 | 6 | 1(16.7%) | 5(83.3%) | |
| Pathological LN Staging (Post-Operative) | ypN0 | 27 | 18(66.7%) | 9(33.3%) | P < 0.001** |
| | ypN1/ ypN2/ ypN3 | 68 | 16(23.5%) | 52(76.5%) | |
| Molecular subtypes | Luminal A | 36 | 19(52.8%) | 17(47.2%) | P < 0.05* |
| | Luminal B | 22 | 9(27.3%) | 13(59.1%) | |
| | HER2-enriched | 17 | 3(17.6%) | 14(82.3%) | |
| | Triple-negative | 20 | 3(15%) | 17(85%) | |
| Response to neoadjuvant chemotherapy | No response | 28 | 4(14.3%) | 24(85.7%) | P < 0.001** |
| | Partial response | 42 | 13(31%) | 29(69%) | |
| | Pcr | 25 | 17(68%) | 8(32%) | |
| Total | | 95 | 34 (35.8%) | 61 (64.2%) | |

**YTHDF1 immunohistochemical results:** The expression exhibited cytoplasmic localization. High YTHDF1 expression was observed in 59 out of 95 (62.1%) cases of breast ductal carcinoma. High levels of YTHDF1 expression were significantly associated with clinical staging (tumor and nodal: P < 0.05/ P < 0.001l), postoperative pathological staging (tumor and nodal: P < 0.001 each) and tumor grade (P < 0.05). The pathological complete response (pCR) was significantly associated with low YTHDF1 expression (P < 0.05). This was detailed in table (6).

**Table (6):** Relation of YTHDF1with clinicopathological parameters of study cases

| Clinicopathological variables | | | YTHDF1 | | Test of Significance |
|---|---|---|---|---|---|
| | | | Low | High | |
| Age Group | < 50 | 40 | 14(35.0%) | 26(65.0%) | P= .624 |
| | ≥ 50 | 55 | 22(40.0%) | 33(60.0%) | |
| Tumor Grade | I | 8 | 5(62.5%) | 3(37.5%) | P < 0.05* |
| | II | 46 | 17(37%) | 29(63%) | |
| | III | 41 | 14(34.1) | 27(65.9%) | |
| Clinical Tumor Staging (Before neoadjuvant Therapy) | T1 | 11 | 8(72.7%) | 3(27.3%) | P < 0.05* |
| | T2 | 38 | 18(47.4%) | 20(52.6%) | |
| | T3 | 36 | 8(22.2%) | 28(77.7%) | |
| | T4 | 10 | 2(20%) | 8(80%) | |
| Clinical LN Staging (Before neoadjuvant therapy | N 0 | 8 | 7(87.5%) | 1(12.5%) | P < 0.001** |
| | N 1/ N2/ N3 | 87 | 29(33.3%) | 58(66.7%) | |
| Pathological Tumor Staging (Post-Operative) | ypT0 | 27 | 19(70.4%) | 8(29.6%) | P < 0.001** |
| | ypT1 | 28 | 11(39.3%) | 17(60.7%) | |
| | ypT2 | 15 | 3(20%) | 12(80%) | |
| | ypT3 | 19 | 2(10.5%) | 17(89.5%) | |
| | ypT4 | 6 | 1(16.7%) | 5(83.3%) | |
| Pathological LN Staging (Post-Operative) | ypN0 | 27 | 17(63.0%) | 10(37.0%) | P < 0.001** |
| | ypN1/ ypN2/ ypN3 | 68 | 19(27.9%) | 49(72.1%) | |
| Molecular subtypes | Luminal A | 36 | 18(50.0%) | 18(50.0%) | P= .071 |
| | Luminal B | 22 | 6(27.3%) | 16(72.7%) | |
| | HER2-enriched | 17 | 8(47.1%) | 9(52.9%) | |
| | Triple-negative | 20 | 4(20.0%) | 16(80.0%) | |
| Response to neoadjuvant chemotherapy | No response | 28 | 5(17.8%) | 23(82.1%) | P < 0.05* |
| | Partial response | 42 | 15(35.7%) | 27(64.3%) | |
| | pCR | 25 | 16(64%) | 9(36%) | |
| Total | | 95 | 36 (37.9%) | 59 (62.1%) | |

**Relation between responses to neoadjuvant chemotherapy (NACT) with clinicopathological parameters:**
No response to NAC was seen in 28/95(29.5%) of study cases. Partial response was detected in 42/95 (44.2%). The pathological complete response (pCR) was seen in 25/95(26.3%) of the breast carcinoma cases. The pathological complete response (pCR) was significantly higher in cases with low grade (P < 0.001), early clinical tumor and nodal stage (P < 0.001), negative SLC7A11 expression (P < 0.001), high ACSL4 level (P < 0.001), negative HNRNPA2B1 (P < 0.001) and low YTHDF1 expression (P < 0.05) as detailed in table (7).

**Table (7):** Relation of response to NACT with clinicopathological parameters of study cases

| Clinicopathological variables | | | Response to neoadjuvant therapy | | | Test of Significance |
|---|---|---|---|---|---|---|
| | | | No | Partial | Complete | |
| Age Group | < 50 | 40 | 13(32.5%) | 16(40.0%) | 11(27.5%) | P= .840 |
| | ≥ 50 | 55 | 15(27.3%) | 26(47.3%) | 14(25.5%) | |
| Tumor Grade | I | 8 | 1(12.5%) | 2(25.0%) | 5(62.5%) | P < 0.001** |
| | II | 46 | 7(15.2%) | 28(60.9%) | 11(23.9%) | |
| | III | 41 | 20(48.8%) | 12(29.3%) | 9(22.0%) | |
| Clinical Tumor Staging (Before neoadjuvant Therapy) | T1 | 11 | 1(9.1%) | 2(18.2%) | 8(72.7%) | P < 0.001** |
| | T2 | 38 | 6(15.8%) | 19(50.0%) | 13(34.2%) | |
| | T3 | 36 | 15(41.7%) | 17(47.2%) | 4(11.1%) | |
| | T4 | 10 | 6(60.0%) | 4(40.0%) | 0(0%) | |
| Clinical LN Staging (Before neoadjuvant therapy | N 0 | 8 | 0(0%) | 2(25.0%) | 6(75.0%) | P < 0.001** |
| | N 1/ N2/ N3 | 87 | 28(32.2%) | 40(46.0%) | 19(27.8%) | |
| Molecular subtypes | Luminal A | 36 | 7(19.4%) | 19(52.8%) | 10(27.8%) | P= .07 |
| | Luminal B | 22 | 7(31.8%) | 9(40.9%) | 6(27.3%) | |
| | HER2-Enriched | 17 | 8(47.1%) | 5(29.4%) | 4(23.5%) | |
| | Triple-Negative | 20 | 6(30.0%) | 9(45.0%) | 5(25%) | |
| SLC7A11 | Negative | 35 | 5 (14.3%) | 14(40.0%) | 16(45.7%) | P < 0.001** |
| | Positive | 60 | 23(38.3%) | 28(46.7%) | 9(15.0%) | |
| ACSL4 | Low | 46 | 22(47.8%) | 19(41.3%) | 5(10.9%) | P < 0.001** |
| | High | 49 | 6(12.2%) | 23(46.9%) | 20(40.8%) | |
| HNRNPA2B1 | Negative | 34 | 4(11.8%) | 13(38.2%) | 17(50%) | P < 0.001** |
| | Positive | 61 | 24(39.3%) | 29(47.5%) | 8(13%) | |
| YTHDF1 | Low | 36 | 2(5.6%) | 17(47.2%) | 17(47.2%) | P < 0.05* |
| | High | 59 | 26(44.1%) | 25(42.4%) | 8(13.6%) | |
| Total | | 95 | 28 (29.5%) | 42 (44.2%) | 25 (26.3%) | |

**Relation between study markers:** SLC7A11 positive expression showed high significant correlation with HNRNPA2B1 (rho= .472) (P<0.001) and YTHDF1 (rho=. 483) (P<0.001). ACSL4 high expression showed high significant inverse correlation with HNRNPA2B1 (rho= -.637) (P<0.001) and YTHDF1 (rho= -0.627) (P<0.001).

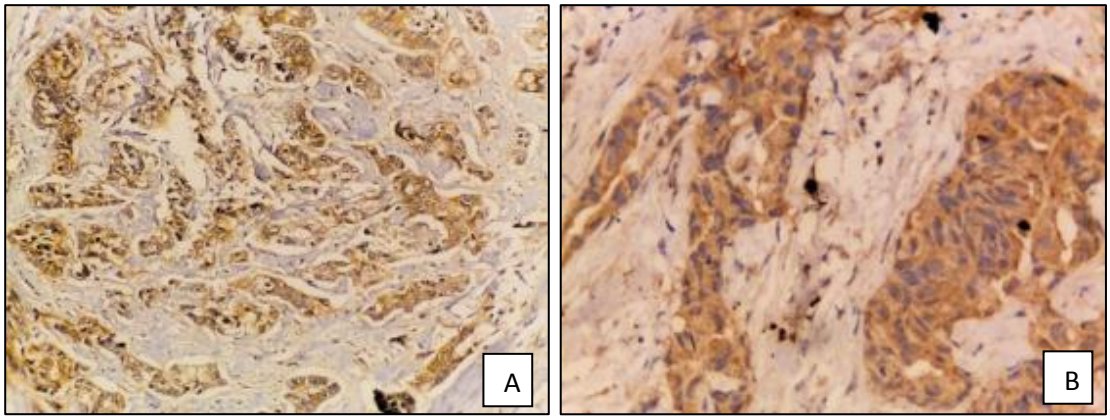


**Figure (1):** (A) Positive SLC7A11 cytoplasmic expression in grade II IDC (ABC ×200). (B) Positive SLC7A11 cytoplasmic expression in grade III IDC (ABC× 400).

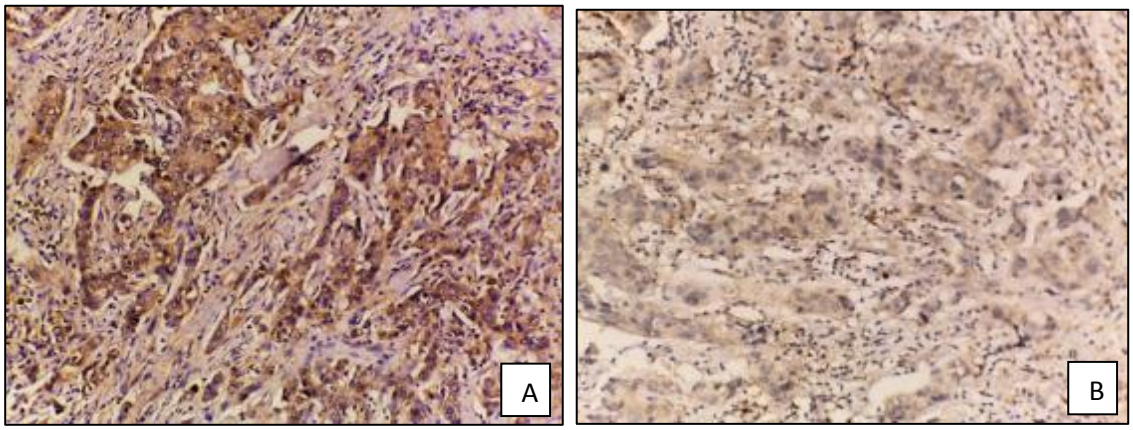


**Figure (2):** (A) High ACSL4 cytoplasmic expression in grade II IDC (ABC×200). (B) Low ACSL4 cytoplasmic expression in grade III IDC (ABC× 400).

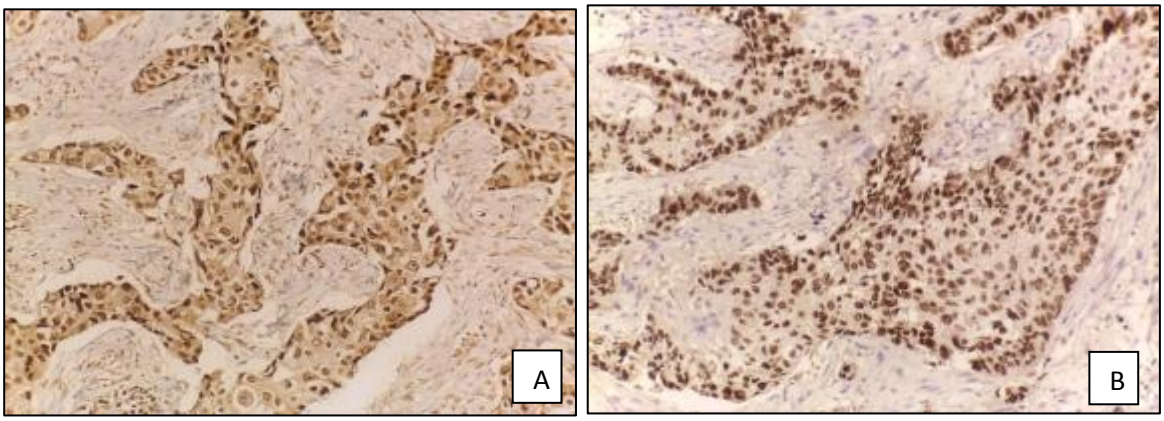


**Figure (3):** (A) Positive HNRNPA2B1nuclear expression in grade II IDC (ABC×400). (B) Positive HNRNPA2B1 nuclear expression in grade III IDC (ABC× 400).

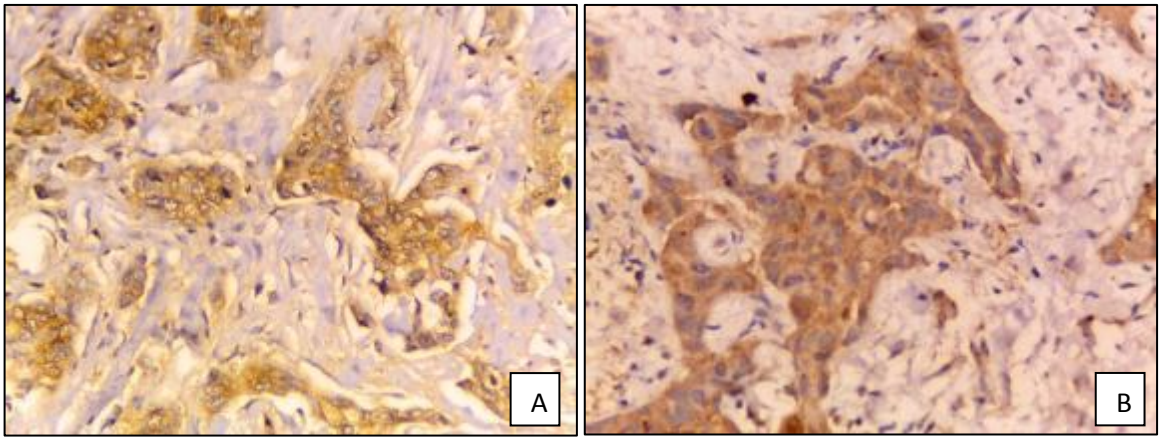


**Figure (4):** (A) High YTHDF1cytoplasmic expression in grade II IDC (ABC×400). (B) High YTHDF1cytoplasmic expression in grade III IDC (ABC× 400).

## DISCUSSION

Breast cancer remains a major public health issue in Egypt, with increasing incidence rates, earlier age of diagnosis and healthcare disparities. Neoadjuvant therapy is considered now corner stone strategy for treatment approach for most of breast cancer patients, offering a way to reduce tumors and assess breast-conserving surgeries [(14)].

Ferroptosis is a distinct form of programmed cell death, characterized by the accumulation of lipid peroxides to cytotoxic levels, primarily driven by iron-dependent oxidative stress. This process is believed to play a crucial role in cancer biology and has emerged as a promising target for cancer therapy. Recent research efforts are focused on identifying the signaling pathways involved in ferroptosis. Additionally, many studies aim to explore the connection between ferroptosis and resistance to chemotherapy [(2)].

The current study aimed to investigate the immunohistochemical expression of ferroptosis markers (SLC7A11 and ACSL4) in breast invasive ductal carcinoma among Egyptian female patients and explore their relation to variable responses to Neoadjuvant chemotherapy whether failed response, partial response or pathological complete response in addition to their relation to different clinicopathological data. Moreover, the study aimed to investigate the relation between ferroptosis markers (SLC7A11 and ACSL4) and N6-methyladenosine (m6A) regulators (HNRNPA2B1, YTHDF1) in breast invasive ductal carcinoma.

SLC7A11 serves as a key modulator of ferroptosis in cancer cells, primarily through its role in modulating cellular cysteine and glutathione (GSH) levels. SLC7A11 facilitates the import of cysteine into the cell in exchange for glutamate. Cysteine serves as an essential precursor for the synthesis of GSH, a pivotal antioxidant that neutralizes lipid-reactive oxygen species (ROS), thus playing a protective role against ferroptosis [(15)].

In the current study, SLC7A11 positive expression was detected in 63.2 % of breast ductal carcinoma cases. Positive SLC7A11 expression showed statistically significant linear correlation with tumor grade, clinical tumor staging, clinical LN staging, pathological tumor and nodal staging (postoperative) and molecular subtypes. The pathological complete response (pCR) was significantly associated with negative SLC7A11 expression ($P<0.001$), indicating a link to ferroptosis. These results match with other studies. The study of **Nath *et al.*** [(5)] revealed high SLC7A11 mRNA and protein expression in breast cancer and its correlation with higher tumor grades, indicating its potential role in cancer progression. High SLC7A11 protein expression was notably observed in aggressive subtypes of breast cancer as Triple Negative (TN) BC.

**Azizi *et al.*** [(15)] demonstrated that in vivo, treatment with SLC7A11 inhibitors slowed tumor growth in breast cancer xenograft models and that histological analysis of tumor tissue revealed increased markers of ferroptosis, such as lipid peroxidation and decreased GPX4 activity, confirming the induction of ferroptosis in vivo. SLC7A11 inhibitors could sensitize breast cancer cells to ferroptosis suggesting that SLC7A11 mediated ferroptosis may serve as a complementary mechanism to enhance the effectiveness of chemotherapy in drug-resistant breast cancer. The study of **Xu *et al.*** [(16)] declared that uncarboxylated osteocalcin (GluOC) treatment in TNBC induces the expression of SLC7A11, which increased glutathione levels enhancing resistance to ferroptosis. This mechanism of ferroptosis resistance provides cancer cells with a survival advantage, particularly in the context of oxidative stress. GluOC upregulate SLC7A11 level through the WWP1/PTEN/PIK3CA/AKT signaling pathway.

**Luo *et al.*** [(17)] found that Tanshinone IIA (Tan IIA) promoted ferroptosis in breast cancer by down regulating SLC7A11**.** (Tan IIA) destabilizes SLC7A11 by promoting SUMOylation, a post-translational modification. The study of **Ma *et al.*** [(18)] revealed that the combined use of Apatinib and Paclitaxel as a potential therapeutic approach in TNBC sensitized the malignant cells to ferroptosis in xenografts through SLC7A11 downregulation leading to reduced GSH levels and decreased antioxidant capacity in TNBC cells inducing ferroptosis. **Yuan *et al.*** [(19)] detected that Icariside II effectively triggered ferroptosis in ovarian cancer cells through downregulation of SLC7A11 leading to an accumulation of lipid peroxides, iron overload, and depletion of GSH, key events that drive ferroptosis.

ACSL4 is a critical enzyme mediating the synthesis of polyunsaturated fatty acids which constitute essential base for formation of lipid peroxides. High levels of ACSL4 contribute to ferroptosis susceptibility, and its downregulation is known to protect cells from ferroptosis [(20)].

In the present study, ACSL4 (ferroptosis inducer) high expression was observed in 51.6% breast ductal carcinoma cases. Elevated ACSL4 expression demonstrated a statistically significant inverse correlation with clinical staging (tumor and nodal), tumor grade and postoperative pathological tumor and nodal staging .The pathological complete response (pCR) was significantly associated with high ACSL4 levels indicating a link to ferroptosis. In the same literature, **Sha *et al.*** [(21)] demonstrated that high ACSL4 expression in breast cancer was associated with pCR and distant metastasis-free survival. The recent study of **Han *et al.*** [(22)] revealed that medium-chain fatty acids (MCFAs) enhanced the sensitivity of breast cancer cells to ferroptosis through upregulation of ACSL4. **Zeng *et al.*** [(6)] declared that inhibition of cyclin-dependent kinase 1 overcome oxaliplatin resistance in colorectal cancer by promoting ACSL4-mediated ferroptosis. **Sun *et al.*** [(23)] detected that increased HMOX1 overcome

chemotherapy resistance in small-cell lung cancer through mic14 regulation, which leads to observed upregulation of ACSL4 and downregulation of GPX4 and SLC7A11 levels. **Wang *et al.*** [24] observed that inhibition of ferroptosis through TRIM37-mediated degradation of ACSL4 contributes to cervical cancer progression. **Jiang *et al.*** [25] approved that the key mechanism through which VIPAS39 confers ferroptosis resistance in epithelial ovarian cancer. VIPAS39 interacts with ACSL4, facilitating its transport out of the cells via vesicular trafficking, which reduces the intracellular levels of ACSL4 and limits its involvement in lipid peroxidation, thereby protecting ovarian cancer cells from ferroptosis.

Heterogeneous nuclear ribonucleoprotein A2B1 (HNRNPA2B1) is considered multifunctional RNA-binding protein implicated in various aspects of cancer biology, including tumorigenesis, tumor progression, metastasis and chemoresistance. Its acts as an m6A reader and regulator mRNA translation and splicing [26].

In the present work, HNRNPA2B1 positive expression was detected in 64.2% of breast ductal carcinoma cases. HNRNPA2B1 positive expression showed statistically significant association with clinical staging (tumor and nodal), post-operative pathological staging (tumor and nodal) tumor grade and molecular types. The pathological complete response (pCR) was significantly associated with negative HNRNPA2B1expresion. In the same literature**, Ayoufu *et al.*** [8] detected high significant expression of HNRNPA2B1 in breast cancer and its relation with tumor staging, grading, immune cell infiltration in the tumor microenvironment, poor prognosis and aggressive disease in breast cancer patients. **Gao *et al.*** [27] demonstrated that upregulated HnRNPA2B1 in breast cancer through activation of STAT3 pathway promoted the proliferation of MCF-7 cells. **Wang *et al.*** [28] observed that HnRNPA2B1 expression was significantly upregulated in gastric carcinoma, particularly in GC cell lines exhibiting multidrug resistance (MDR). Silencing HNRNPA2B1 enhanced the sensitivity of gastric cancer cells to chemotherapy.

In the current study, YTHDF1 high expression was detected in 62.1% of breast ductal carcinoma cases. High YTHDF1 expression demonstrated a statistically significant association with tumor grade, clinical staging (tumor and nodal) as well as postoperative pathological tumor and nodal stages. Notably, a significant correlation was also identified between low YTHDF1 expression and pathological complete response (pCR). In the same literature, **Chen *et al.*** [29] declared that YTHDF1 is highly expressed in breast cancer tissues and cell lines and correlated with larger tumor size, lymph node invasion, distant metastasis and poor overall survival. They explained that YTHDF1 facilitates breast cancer progression by promoting the translation of FOXM1 mRNA in an m6A-dependent manner. **Sun *et al.*** [30] approved similar results concerning YTHDF1 overexpression in breast cancer and its association with chemoresistance and shorter overall survival. They also explained that knockdown of YTHDF1 impairs DNA repair mechanisms, increasing sensitivity to chemotherapeutic agents such as Adriamycin, Cisplatin, and Olaparib. Similarly, the study of **Wu *et al.*** [31] approved the critical oncogenic and prognostic role of YTHDF1 in progression of triple-negative breast cancer.

Regarding the relation between ferroptosis markers and each HNRNPA2B1 and YTHDF1. SLC7A11 positive expression showed high significant correlation with HNRNPA2B1 (rho= .472) (P<0.001) and YTHDF1 (rho=. 483) (P<0.001). ACSL4 high expression showed high significant inverse correlation with HNRNPA2B1 (rho= -.637) (P<0.001) and YTHDF1 (rho= -.627) (P<0.001). Limited studies have handled the relation between M6A modification regulators and ferroptosis in cancer. **Zheng *et al.*** [32] demonstrated that HNRNPA2B1 is overexpressed in pancreatic cancer tissues and is associated with increased resistance to ferroptosis. The overexpression of HNRNPA2B1 was shown to suppress Transferrin Receptor (TFRC) expression, thereby reducing cellular iron uptake and inhibiting ferroptotic cell death. Similarly, **Jiang *et al.*** [33] elucidated that HNRNPA2B1 was associated with chemoresistance and inhibition of ferroptosis in endometrial carcinoma through m6A modification of FOXM1**.** Furthermore, **Xu *et al.*** [34] approved that METTL3, a key m6A methyltransferase, leads to m6A modification of SLC7A11 increasing its expression with subsequent reduced ferroptosis in lung adenocarcinoma.

Concerning responses to neoadjuvant chemotherapy, the current study revealed that no response to NACT was seen in 29.5% of study cases. Partial response was detected in 44.2%. Pathological complete response was seen in 26.3% of the breast carcinoma cases. Pathological complete response was significantly higher in cases with low grade, low clinical tumor stage and low clinical nodal stage. Pathological complete response was significantly associated with ferroptosis occurrence (low SLC7A11 and high ACSL4). These observations suggest a potential role of SLC7A1 and ACSL4 in promoting resistance to neoadjuvant chemotherapy in breast ductal carcinoma.

Based on the preceding results, this study highlighted on the possible role of ferroptosis markers, SLC7A11 and ACSL4 in influencing the sensitivity or resistance of breast invasive ductal carcinoma cells to neoadjuvant chemotherapy. This raises the question about the possibility of modulating novel therapeutic strategies aimed to induce ferroptosis in breast ductal carcinoma. In addition, the current work may highlight the possibility of M6A modification of ferroptosis regulators SLC7A11 and ACSL4 by HNRNPA2B1,

YTHDF1, which may facilitate ferroptosis induction in breast ductal carcinoma.

## CONCLUSION

The expression of ferroptosis regulators SLC7A11 and ACSL4 was found to significantly impact the response to neoadjuvant chemotherapy, suggesting possible potential for developing novel therapeutic strategies that modulate ferroptosis to overcome chemotherapy resistance in breast cancer. The findings of the present study further propose that m6A modifications of ferroptosis regulators SLC7A11 and ACSL4, mediated by RNA-binding proteins such as HNRNPA2B1 and YTHDF1, could serve as a mechanism to induce ferroptosis in breast cancer cells. Our results may highlight that previous markers may provide potential predictive indicators and promising therapeutic targets for breast invasive ductal carcinoma.

**No funding.**

**No conflict of interest.**

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