Original Article
Running Title: FAS Expression and NAC in TNBC
Received: June 17, 2026; Accepted: September 27, 2026

Fatty Acid Synthetase and its Role in the Pathological Response after Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer

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Abstract
Background: Triple-negative breast cancer (TNBC) has few targeted treatment choices, reflecting the need for biomarkers that may help in predicting the response to neoadjuvant therapy (NAT).The present study aimed to evaluate fatty acid synthetase (FAS) expression in TNBC and to assess its association with pathological response to NAC.
Method: A retrospective study included 145 patients with TNBC who received NAC followed by surgery from 2019 to 2023. FAS expression was determined using immunohistochemistry and scores from 0 to 3+ indicating low (scores 0–1+) or high (scores 2–3+). Associations between FAS expression, clinical features, and pathological response were analyzed using the chi-square test. Statistical analyses were performed using SPSS 22.0 and MedCalc, with $P<0.05$ considered statistically significant.
Results: A total of 124 patients were eligible and included in the study. High FAS expression was detected in 29.8% of the cases, while 70.2% had low expression. Among the 53 patients who achieved a pathological complete response (pCR), 79.2% had low FAS expression compared with 20.8% with high expression. Low FAS expression was not significantly correlated with the clinical parameters studied. In contrast, high FAS expression was significantly correlated with tumor size, grade, lymph node involvement, menopausal status, Ki-67 levels, and pCR ($P< 0.05$).
Conclusion: High FAS expression is notably associated with higher histological grade, larger tumor size, lymph node positivity, higher Ki-67 expression, and a lower rate of pCR after NAC.

Keywords: Triple negative breast neoplasms, Neoadjuvant therapy, Treatment outcome, Biomarkers

Introduction

Triple-negative breast cancer (TNBC) is a specific type of breast cancer (BC) distinguished by the lack of the following tests: estrogen receptor (ER), progesterone receptor (PR), and overexpression of the human epidermal growth factor receptor 2

(HER2). This subtype represents for about 10%-15% of all BCs.[1]

TNBC is known for its unique patterns of metastasis, aggressive nature, distinct molecular characteristics, and generally poor survival outcomes.[2] For instance, the 5-year survival rate for those with TNBC is 77.1%, which contrasts sharply with the 94.4% rate for luminal BCs. Because of the lack of specific targeted therapies for TNBC, chemotherapy remains the primary therapy option, even as immune-based therapies continue to grow.[3]

The National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant chemotherapy (NAC) as the preferred approach of operable TNBC cases, especially when the tumor measures 2 cm or more (≥T2) or metastasis to axillary lymph nodes (≥cN1). NAC may also be considered for tumors< 2 cm without lymph node involvement (T1 N0) and for locally advanced disease.[4]

Pathologic complete response (pCR) is frequently used as an endpoint in various studies and is linked to improved outcomes. There is a critical need to maximize responses to NAC using well-chosen predictive markers. Selecting the right patients based on these markers could lead to better survival outcomes.[5]

Fatty acid synthetase (FAS) is an enzyme that plays a key role in producing fatty acids and is crucial for tumor growth and survival, particularly in lipogenic tumors.[6] It is upregulated in various malignant tumors, including those of the breast, ovary, colon, prostate, lung, and liver. Many studies have looked into how FAS affects survival rates.[7]

While the prognostic value of FAS has been assessed in various BCs, there is less research focused specifically on its role in TNBC.[8] Therefore, the present study aimed to examine FAS expression in TNBC patients and how it relates to the pathological response following NAT.

Patients and Methods

Type of study

This retrospective study (no randomization was performed, and so no randomization method or block size was applicable) included female patients with TNBC who were diagnosed in the pathology department and treated in the Medical, Clinical, and Surgical Departments at the Faculty of Medicine, Zagazig University, Egypt, from January 2019 to December 2023.

Inclusion criteria

We included women aged 18 and older who had a confirmed diagnosis of TNBC, with non-metastatic disease, tumor size of at least cT2 and/or cN1, and who were considered to have locally advanced cancer.

Immunohistochemistry (IHC)

After a true-cut biopsy and examining the histopathology, we checked and completed any missing molecular studies. This included hormone assays, HER2 expression, Ki-67, and FAS. A diagnosis of TNBC was made when ERand PR expression were both below 1% by IHC. Additionally, the HER2 status had to be negative (0 to 1+ by IHC, or IHC 2+ with negative fluorescence in situ hybridization (FISH), following American Society of Clinical Oncology and College of American Pathologist ASCO/CAP guidelines.[9]

A consultant pathologist stained the breast tissue using FAS. They worked with 3-µm sections of tissue through IHC. After deparaffinizing and rehydrating the slides with ethanol solutions, they extracted the antigen using a Tris-EDTA buffer solution at pH 8.9. They blocked peroxidase activity with hydrogen peroxide (10%) during three 3-minute treatments. FAS was the main antibody applied, followed by hematoxylin staining. If more than 10% of the tumor cells stained positive for FAS, it was considered a positive result, with intensity rated from 0 to 3 (0 = no staining, 1 = 1-20%, 2 = 21-40%, and 3 = 40% or more). For analysis, FAS staining of 0–1+ was classified as low expression, whereas

staining of 2–3+ was categorized as high expression.[10]

Data collection

The clinical data, such as performance status, age, menopausal status, tumor size, and lymph node involvement, were collected. Moreover, true-cut pathology features like the type of pathology (invasive or non-invasive BC), tumor grade, size, ER, PR, Ki-67, and FAS are assessed through medical files and pathology reports. We also documented the pathology response, noting both (pCR and non-pCR).

Treatment protocol

The NCCN guidelines were the main treatment protocols used. After the staging work-up and clinical evaluation, the multidisciplinary team decided on the treatment protocol. Two chemotherapy regimens were implemented: the classic approach of adriamycin and cyclophosphamide protocol (AC×4) followed by weekly paclitaxel for 12 weeks and a dose-dense variant. Both with appropriate premedication. In the classic protocol, doxorubicin 60 mg/m² was given as an IV push, followed by cyclophosphamide 600 mg/m² IV in 250 mL of normal saline over a period of 20 minutes to 1 hour. This cycle was repeated every 21 days for four total cycles. After that, paclitaxel at 80 mg/m² was administered IV in 100-500 mL of normal saline over an hour on a weekly basis for 12 weeks. For the dose-dense version, doxorubicin was still 60 mg/m² as an IV push, followed by the same dosage of cyclophosphamide, and then filgrastim (G-CSF) was given from day 3 to day 6 of chemotherapy, with this regimen repeated every 14 days for four cycles. Lastly, paclitaxel was administered at 175 mg/m² IV in 500 mL of normal saline over 3 hours, followed by G-CSF from day 3 to day 6, which was also repeated every 14 days for four cycles.[4]

Surgical management

After completing NAC, a staging workup is performed. If the results are favorable, the patient undergoes surgical treatment, which may include either a breast-conserving surgery or a modified radical mastectomy with axillary clearance.

Pathological response

The pathological response was assessed using hematoxylin and eosin (H&E) staining. This response was classified as either a pCR, indicating no residual invasive carcinoma in the breast tissue and axillary lymph nodes, or non-pCR, which indicated some residual invasive disease.[11]Figure 1 illustrates the flowchart.

Ethical consideration

The approval for the research proposal was obtained from the Institutional Review Board (IRB) of Zagazig University Hospital before commencing the study. The data were securely stored in a locked location without any patient identifiers on the data sheets. The data collection forms were linked to the data via a serial code number. The informed consent was waived due to the retrospective nature of the study.

Statistical analysis

Statistical analyses were carried out using SPSS 22.0 for Windows (IBM, Inc., Chicago, IL, USA) and MedCalc for Windows (MedCalc Software bvba, Ostend, Belgium). Associations between FAS expression, pathological response, and clinicopathological characteristics were assessed using the chi-square test. A two-sided P value < 0.05 was considered statistically significant.

Results

Out of the 145 patients included in the study, 21 were excluded due to missing data. Most patients were 40 years old or younger, and a significant proportion were premenopausal (85.5%). IDC was the most common type of cancer observed. Notably, 91.1% of the patients had high Ki-67 levels. Additionally, high FAS expression was found in 29.8% of the patients, with 42.7% achieving a pCR. Table 1 provides an overview of the clinicopathological features.

Among the 53 patients who achieved pCR, 42 (79.2%) had low FAS expression, while

11 (20.8%) had high FAS expression, a statistically significant difference (P< 0.001) as shown in Table 2.

In the TNBC group, 29.8% (37 out of 124) of patients had high FAS expression levels, while 70.2% (87 out of 124) had low levels. Table 3 shows the relationships between pCR, FAS expression, and various clinical and pathological features. Low FAS expression did not show significant associations with the studied characteristics. However, high FAS expression was significantly linked to tumor size, histological grade, lymph node involvement, menopausal status, and Ki-67 (P < 0.05).

Discussion

The present study revealed that 29.8% of TNBC patients had high FAS expression, which was associated with aggressive tumor features such as younger age, menopausal status, lymph node involvement, larger tumor size, higher histological grade, and elevated Ki-67 levels.

These findings are consistent with previous research findings ranging from 24.1% to 32.9%.[8,10,12] Variations in reported expression rates may be due to variances in study demographics, sample sizes, IHC assessment methodologies, scoring systems, and threshold values for FAS overexpression.

In the case-control study by Pizato et al., serum FAS levels were significantly higher in premenopausal women (N = 18) compared with postmenopausal women (N = 29), with a statistically significant difference (P = 0.026).[13]

Giro et al. carried out a retrospective study involving 100 patients diagnosed with TNBC. Their findings showed a correlation between FAS expression and the probability of lymph node involvement, as well as higher tumor grades. In another study, Jiang et al. found a significant correlation between lymph node involvement and TNM staging in a group of 218 patients with TNBC, while evaluating the expression of FAS and MET.[8]

In two distinct studies, BC patients with tumors < 2 cm without lymph node involvement had a four-fold higher risk of death when associated with FAS over-expressed.[14]

When it comes to FAS expression levels and histological grading, the results are inconclusive. The present study discovered a positive correlation, in line with the results of Giro et al.,[10] but contradict to the study by Yoshikawa et al., which did not augment this relation. This discrepancy may be related to differences in patient features or sample size.[15]

In five studies involving 855 BC patients, it was found that increased FAS expression was linked to larger tumor sizes. Therefore, using FAS inhibitors could potentially reduce tumor size and improve the efficacy of NAC.[16]

Ki-67, assessed through IHC, serves as a marker for cell proliferation in TNBC. This method is not only cost-effective but also practical for use in various clinical environments.[17]High Ki-67 levels generally refer to a higher probability of early disease recurrence and more disease aggressiveness, which often results in worse survival rates. In a study conducted in Japan, a Ki-67 level greater than 10% was associated with an increased risk of recurrence and worse survival outcomes.[18-23]

A study found that BC patients with negative lymph node involvement showed a nine-fold increased risk of death when they had high Ki-67 levels alongside FAS expression.[14]

Recent research has revealed that lipid metabolism is a key factor in cancer progression. It can supply the extra energy needed for metastasis. While FAS expression is typically low in normal cells, it is significantly expressed in breast, ovarian, prostate, oral, and certain central nervous system cancers and is often linked to poor outcomes. Initial data suggest that inhibiting FAS may lead to programmed

cell death. Thus, FAS has become a promising target, with FAS inhibitors currently undergoing clinical trials.[24,25] Drugs targeting FAS, such as orlistat and cerulenin, belong to the first generation, and TVB-3166 and TVB-2640 are part of the next generation, had been evaluated.[26]

Through our study, the chemotherapy protocols used were derived from NCCN guidelines. Of TNBC patients, 42.7% had achieved pCR; 79.3% had low FAS expression, whereas 20.7% had high FAS expression. Although the pCR results and prior data matched, there has not been much research done on the relationship between FAS expression and NAC response.

Earlier studies revealed that dose-dense chemotherapy can boost the rate of pCR in high-risk patients. However, this study did not show a significant difference between dose-dense and standard chemotherapy approaches. The small number of participants and the few who actually received the dose-dense treatment might have affected these findings. Additionally, financial issues, especially in developing countries, could make it difficult to implement dose-dense protocols into practice.[27]

NAC is the backbone of TNBC treatment either in most of the early stages or locally advanced, given the treatment response's prognostic value and the potential for using innovative, promising adjuvant therapies to treat the non-pCR group. Attaining pCR is correlated with a favourable outcome, comparable to other subtypes of BC, and serves as an indicator of survival.[28]

Regretfully, a small percentage of TNBC patients benefit little or not at all from chemotherapy. This aggressive subgroup of chemo-resistant patients exhibits high rates of failure, a heightened risk of metastases, and a dearth of identified molecular targets for therapeutic intervention. In addition, these patients received multiple doses of chemotherapy with minimal benefit, suggesting that predictive biomarkers are necessary to avoid needless toxicity and expenses.[29,30]

Numerous studies have explored the predictive value of classic clinicopathologic characteristics as histological grade, tumor size, and lymph node involvement for the response to NAC, yielding conflicting results.[31]

There is currently no standard biomarker to predict the response to NAC in TNBC patients. Identifying novel biomarkers at baseline that can distinguish between good and poor responders is crucial for guiding treatment decisions.[32]

One important limitation of this study is the exclusion of 21 patients due to incomplete data, reflecting suboptimal documentation. This may have introduced selection bias and potentially affected the study outcomes. In addition, the retrospective design represents another limitation, as such studies depend on the accuracy and completeness of medical records. The relatively small sample size further limits the generalizability of the findings.

Conclusion

Even with the combination of immune therapy and chemotherapy in treating TNBC, the survival outcome is still not great. Our study focused on figuring out the differences in patients with TNBC treated with NAC based on the level of FAS expression, with the goal of refining treatment choices to enhance patient outcomes. Elevated FAS expression in TNBC is associated with aggressive characteristics, leading to decreased response to NAC. These findings may aid in predicting tumor behavior and improving pre-treatment strategies by considering more intensive NAC or incorporating an extended adjuvant therapy. Furthermore, FAS may represent a potential candidate for targeted therapy, as modulation of the pathway can restore apoptotic signalling and enhance treatment response.

Funding

None declared.

Acknowledgements
I would like to thank the entire medical oncology team for their assistance.

Authors' Contributions
Amrallah Mohammed: idea, data collection, interpretation, and discussion; Yaser Arafat: idea, data collection, interpretation, and discussion; Ahmad BarakatWaley: idea, data collection, interpretation, and discussion; Israi Mahgoub: idea, data collection, interpretation, and discussion; Doa Madour: idea, data collection, interpretation, and discussion; Mohamed Biomy: idea, data collection, interpretation, and discussion; Adel Bakry: idea, data collection, interpretation, and discussion.
All authors have read and approved the final version, and agreed to be accountable for all aspects of the work and to ensure that questions regarding the accuracy or integrity of any part of the work are appropriately reviewed and resolved.

Conflict of Interest
None declared.

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Table1. Clinicopathological features of the 124 TNBC patients included in the study

Variables	N (%)
Age (years)	69 (55.65)
≤40	46 (37.09)
>40-60	9 (7.26)
≥60	
Menopausal status	106 (85.48)
Premenopausal	18 (14.52)
Post-menopausal	
Pathology	115 (92.74)
IDC	9 (7.26)
Non-IDC	
T	9 (7.26)
T1	59 (47.58)
T2	45 (36.29)
T3	11 (8.87)
T4	
N	7 (5.64)
N0	62 (50.00)
N1	42 (33.87)
N2	13 (10.49)
N3	
Grade	23 (18.54)
I	58 (46.77)
II	43 (34.69)
III	
Ki-67	11 (8.87)
Low	113 (91.13)
High	
FAS expression	87 (70.16)
Low	37 (29.83)
High	
Pathological response	53 (42.74)
pCR	71 (57.26)
Non-Pcr	

TNBC: Triple-negative breast cancer; IDC: Invasive duct carcinoma; T: Tumor size; N: Lymph node status; FAS: Fatty acid synthetase; pCR: Pathological complete response: Ki-67 low (<20%) and high (≥20%); N: Number

Table 2. Distribution of pathological response among TNBC patients according to FAS expression

Variable	**pCR (N=53)**		**Non-pCR (N=71)**		***P* value**
	N	**%**	**N**	**%**	
Low expression FAS N=87	42	79.24	45	63.38	0.001
High expression FAS N=37	11	20.86	26	36.62	

TNBC: Triple-negative breast cancer; pCR: Pathological complete response; FAS: Fatty acid synthetase; N: Number of patients; A *P*-value < 0.05 was considered statistically significant.

Table 3. Relationship between pCR, FAS expression, and clinicopathological characteristics in TNBC patients

Variables	Low expression-FAS (No=87)					High expression-FAS (No=37)				
	pCR No = 42		Non-pCR No= 45		*P* value	pCR N=11		Non-pCR No= 26		*P* value
	No	%	No	%		No	%	No	%	
Age (years)										
≤40	21	50.00	24	53.33		5	45.46	19	73.07	
>40-60	18	42.85	19	42.22	0.8	4	36.36	5	19.23	0.07
≥60	3	7.15	2	4.45		2	18.18	2	7.70	
Menopausal status										
Premenopausal	34	80.95	42	93.33	0.3	9	81.81	21	80.76	0.02
Postmenopausal	8	9.05	3	6.67		2	18.19	5	19.24	
Pathology										
IDC	39	92.85	43	95.55	0.6	10	90.90	24	92.30	0.21
Non-IDC	3	7.15	2	4.45		1	9.10	2	7.70	
Grade										
I	13	30.95	3	6.66	0.2	2	18.19	5	19.23	0.04
II	21	50.00	30	66.66		3		4	15.38	
III	8	19.05	12	26.68		27.27		17	65.39	
						6				
						54.54				
T										
T1	2	4.76	4	8.88		1	9.10	2	7.70	
T2	37	88.09	14	31.11	0.1	4		4	15.38	0.03
T3	2	4.76	24	53.33		36.36		13	50.00	
T4	1	2.39	3	6.68		6		7	26.92	
						54.54				
						00.00				
N										
N0	3	7.15	1	2.22		1	9.10	2	7.70	
N1	33	78.57	15	33.33		8		6	23.07	
N2	4	9.52	22	48.88	0.4	72.71		14	53.85	0.003
N3	2	4.76	7	15.57		2		4	15.38	
						18.19				
						0				
						0.00				
Ki67										
Low	3	7.14	2	4.45	0.5	4	36.36	2	7.70	0.03
High	39	92.86	43	95.55		7	63.64	24	92.30	

No.: Number of patients; pCR: Pathological complete response; IDC: Invasive duct carcinoma; T: Tumor size; N: lymph node status; FAS: Fatty acid synthetase. Ki-67 low (<20%) and high (≥20%). P value < 0.05 is considered statistically significant.

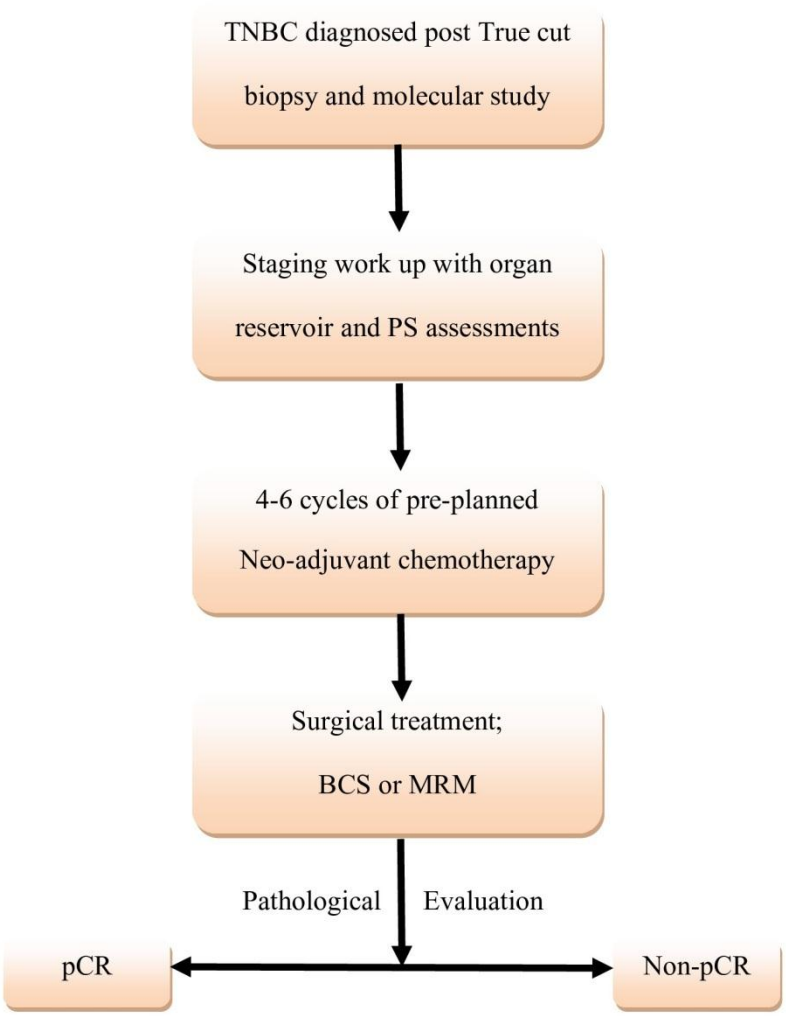

Figure1. This figure shows the flow chart of our study.
TNBC: Triple negative breast cancer; NAC: Neoadjuvant chemotherapy; BCS: Breast conserving surgery; MRM: Modified radical mastectomy; pCR: Complete pathological response