DOI:10.31557/APJCC.2026.11.5.769

RESEARCH ARTICLE

Comparative Analysis of Hypoxia-Inducible Factor-1α and Interleukin-6 Levels in Triple-Negative and Luminal Breast Cancer

Saddek Yahia[1]*, Zineb Tahari[1,2], Asmahane Medjdoub[1,2], Tewfik Sahraoui[1]

[1]Biology of Development and Differentiation Laboratory, Ahmed Ben Bella University, Oran 1, Oran, Algeria. [2]Department of Life and Environmental Sciences, University of Science and Technology of Oran, Mohamed-Boudiaf, Oran, Algeria.

Abstract

Introduction: Breast cancer (BC) is a heterogeneous disease classified into distinct biological subtypes. This study aimed to compare the circulating levels of hypoxia-inducible factor-1alpha (*HIF-1α*) and interleukin-6 (*IL-6*) between triple-negative (TNBC) and luminal BC subtypes and to evaluate their correlation with clinicopathological parameters. **Materials and Methods:** We conducted a retrospective study involving 60 patients. Serum concentrations of *HIF-1α* and *IL-6* were measured using a sandwich ELISA technique. Laboratory analyses were performed blinded to the clinical and pathological data. Normality was assessed using the Shapiro–Wilk test. Since serum *HIF-1α* and *IL-6* concentrations followed a non-normal distribution, the Mann–Whitney U test was used for group comparisons. Correlations between biomarkers and ordinal variables, such as the SBR grade, were evaluated using Spearman's rank correlation coefficient. **Results:** A significant difference in serum *HIF-1α* levels was observed between TNBC and luminal BC, with higher concentrations in the TNBC subtype ($p = 0.04$). Furthermore, a positive correlation was identified between *HIF-1α* levels and SBR grade within the TNBC group ($p = 0.02$, Spearman's rho = 0.57). In contrast, no significant differences in *IL-6* levels were found between the two subtypes, nor were there any significant associations with clinicopathological parameters ($p > 0.05$). **Conclusion:** These findings suggest that serum *HIF-1α* levels are differentially elevated in TNBC and may be associated with its aggressive biological behavior. While these results highlight the potential role of *HIF-1α* in TNBC, further studies on larger cohorts are necessary to confirm these preliminary findings given the limited sample size of this study.

Keywords: breast cancer- hypoxia-inducible factor-1alpha- interleukin-6- luminal- triple negative

Asian Pac J Cancer Care, **11 (5)**, 769-776 Submission Date: 06/01/2026 Acceptance Date: 08/01/2026

Introduction

Breast cancer (BC) is characterized by significant morphological and molecular heterogeneity. Gene expression profiling has identified distinct intrinsic molecular subtypes with different clinical behaviors and therapeutic responses: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2-positive), and triple-negative (TN) subtypes [1, 2].

While luminal tumors generally carry a better prognosis, TNBC defined by the lack of hormone receptors (HR) and HER2 is associated with a highly aggressive clinical course [3]. Due to the absence of these molecular targets, chemotherapy remains the primary systemic treatment option, highlighting an urgent need for new circulating biomarkers to guide therapeutic strategies [4].

The tumor microenvironment plays a critical role in this aggressiveness, particularly through hypoxia and inflammation. Hypoxia-inducible factor-1alpha (*HIF-1α*) is a key transcription factor mediating the cellular response to low oxygen levels [5], It has been reported that intra-tumoral hypoxia is more pronounced and plays a more deleterious role in TNBC than in other subtypes [6]. Parallel to hypoxia, interleukin-6 (*IL-6*) acts as a pleiotropic cytokine involved in the immune response and inflammation [7], Although its role in cell proliferation

Corresponding Author:
Dr. Saddek Yahia
Biology of Development and Differentiation Laboratory, Ahmed Ben Bella University, Oran 1, Oran, Algeria.
Email: saddek.yahia@gmail.com

is complex, elevated *IL-6* levels have been specifically associated with the TNBC phenotype [8, 9].

The interplay between hypoxic signaling and inflammatory cytokines is thought to drive tumor progression and resistance. We hypothesized that the combined evaluation of these two circulating markers could reflect the distinct biological aggressiveness of TNBC compared to luminal subtypes. Therefore, the aim of this study was to compare serum *HIF-1α* and *IL-6* concentrations between TNBC and luminal BC patients from Western Algeria and to correlate these levels with pathological parameters.

Materials and Methods

Ethical Considerations

The study protocol was designed and conducted in strict accordance with international ethical standards, ensuring full compliance with the Declaration of Helsinki and global research ethics guidelines. Formal approval was granted by the Ethical Committee of Batna 2 University, Algeria (Ref: 2024/R/U.B.2/). All participants were fully informed about the study's objectives and provided written informed consent prior to their inclusion.

Study Design and Population

We conducted a retrospective study involving 60 women diagnosed with primary breast cancer (BC) at the University Hospital (EHU) of Oran (Medical Oncology and Gynecology-Obstetrics departments) between October 2020 and February 2022. The cohort consisted of 21 cases of TNBC and 39 cases of luminal subtypes (A and B).

Inclusion Criteria

Confirmed histological diagnosis of BC and availability of pre-treatment serum samples.

Exclusion Criteria

Patients who had received prior chemotherapy, radiotherapy, or any other anti-cancer treatment. Patients with incomplete medical records were also excluded to ensure data integrity.

Clinicopathological Assessment

Pathological parameters, including SBR grade, tumor size, and Ki-67 proliferation index, were retrieved from medical records. Molecular subtypes were determined by immunohistochemistry (IHC) according to standard clinical protocols. TNBC was defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Luminal subtypes were defined by the presence of hormone receptors (ER and/or PR).

Serum Collection and Handling

Venous blood samples were collected via venipuncture in the crease of the arm into plain tubes (without anticoagulants) to obtain serum. After allowing 30 minutes for coagulation at room temperature, samples were centrifuged at 3000 g for 10 minutes. The resulting serum was immediately aliquoted and stored at -80°C for optimum preservation until biochemical analysis.

Biochemical Assays (ELISA)

The quantification of *IL-6* and *HIF-1α* was performed at the Biology of Development and Differentiation Laboratory (Ahmed Ben Bella Oran 1 University) and the Immunology Laboratory of the Institut Pasteur (Oran branch).

Serum levels were determined using commercial sandwich ELISA kits from Sigma-Aldrich (*IL-6*: RAB0306; *HIF-1α*: RAB1057). Following the manufacturer's instructions, serum samples were diluted 2-fold using specific assay diluents. To ensure technical reliability, all standards and samples were analyzed in duplicate, and laboratory personnel were blinded to the clinicopathological data.

Protocol for IL-6 (RAB0306)

Procedure

100 µL of each standard and sample (2-fold dilution) were added to the anti-human *IL-6* coated plate and incubated for 2.5 hours at room temperature with gentle shaking. After four washes with 300 µL of wash solution, 100 µL of biotinylated detection antibody was added for 1 hour.

Detection

HRP-streptavidin (600-fold dilution) was added for 45 minutes. After a final wash, 100 µL of TMB substrate was added for 30 minutes in the dark. The reaction was stopped with 50 µL of Stop Solution, and absorbance was measured at 450 nm.

Performance

The minimum detectable dose (sensitivity) was 3 pg/mL, with an intra-assay coefficient of variation of less than 10% and an inter-assay coefficient of variation of less than 12%.

Protocol for HIF-1α (RAB1057)

Procedure

100 µL of standards (ranging from 0.061 to 15 ng/mL) and samples (2-fold dilution) were incubated for 2.5 hours. Following the wash steps, 100 µL of biotinylated detection antibody was added (1 hour), followed by HRP-streptavidin (300-fold dilution) for 45 minutes.

Detection

TMB substrate was incubated for 30 minutes before adding the Stop Solution, and optical density was measured at 450 nm.

Performance

The minimum detectable dose (sensitivity) was 61 pg/mL, with an intra-assay coefficient of variation of less than 10% and an inter-assay coefficient of variation of less than 12%.

Statistical analysis

Statistical analysis was performed using JASP (version

0.19.1.0). Descriptive statistics were used to summarize clinical and pathological characteristics. The normality of continuous variables was assessed using the Shapiro–Wilk test along with visual inspection of histograms and Q–Q plots. Based on these assessments, appropriate parametric or non-parametric tests were selected for each variable. For normally distributed variables (e.g., Ki-67), group comparisons were performed using the Student's t-test. For variables that did not meet normality assumptions (e.g., *IL-6* and *HIF-1α*), the Mann–Whitney U test was used to compare distributions between groups.

Correlation analyses were conducted using Spearman's rank correlation coefficient (ρ), as some variables, including SBR grade, were treated as ordinal variables. Ties were handled using standard procedures implemented in the software. Given the primary objective of comparing specific markers between molecular subtypes within our cohort (N=60), univariate analyses were prioritized, and multivariable models were not included. A p-value < 0.05 was considered statistically significant.

Results

Clinical and Pathological Characteristics

The mean age of patients was 52.95 ± 11.54 years for the TNBC group (n=21) and 53.53 ± 11.67 years for the luminal group (n=39). Regarding the SBR grade, 47.6% (10/21) of TNBC patients were classified as grade 3, compared with 25.6% (10/39) of luminal patients. Tumor size T2 was the most frequent in both groups, observed in 66.7% (14/21) of TNBC patients and 53.8% (21/39) of luminal patients. Detailed clinicopathological characteristics are summarized in Table 1.

Histological Distribution

The distribution of histological subtypes is detailed in Table 2. Invasive Breast Carcinoma of No Special Type (IBNST) was the predominant subtype in both cohorts, observed in 66.7% (14/21) of TNBC patients and 71.8% (28/39) of luminal patients. Other histological types showed distinct distribution patterns: infiltrating pleomorphic ductal carcinoma (10.3%; 4/39) and infiltrating lobular carcinoma (5.1%; 2/39) were identified exclusively in the luminal molecular class. Conversely, phyllodes tumor (4.8%; 1/21) and infiltrating ductal carcinoma (4.8%; 1/21) were identified only in the TNBC molecular class.

Table 1. Distribution of Patients According to SBR Grade and Tumor Size

Prameters	Luminal % (n)	TNBC % (n)
SBR grade		
1	2.564 (1)	4.762 (1)
2	71.795 (28)	47.619 (10)
3	25.641 (10)	47.619 (10)
Tumor size		
1	20.513 (8)	20 (4)
2	53.846 (21)	65 (14)
3	17.949 (7)	10 (2)
4	7.692 (3)	5 (1)

Table 2. Distribution of TN and Luminal BC Patients by Histological Type

Histological types	TNBC % (n)	Luminal BC % (n)
Non-specific infiltrating breast carcinoma	66.7 (14)	72.5 (28)
Pure mucinous carcinoma	4.8 (1)	2.5 (1)
Phyllode tumor	4.8 (1)	0 (0)
Ductal carcinoma in situ	9.5 (2)	2.5 (1)
Infiltrating ductal carcinoma	4.8 (1)	0 (0)
Metaplastic breast carcinoma	4.8(1)	5 (2)
Infiltrating micro-papillary breast carcinoma	4.8 (1)	2.5 (1)
Infiltrating pleomorphic ductal carcinoma	0 (0)	10 (4)
Infiltrating lobular carcinoma	0 (0)	5 (2)

Biomarker Analysis

No statistically significant difference in serum *IL-6* levels was observed between TNBC and luminal BC patients (Mann–Whitney U test, p = 0.21). *IL-6* levels were highly skewed in both groups, with median values of 8.62 (0–186.46) in TNBC and 0 (0–115.69) in luminal BC patients. The mean *IL-6* levels were 228.22 ± 490.07 in TNBC and 78.08 ± 179.04 in luminal BC patients (Table 3).

A significant difference was observed in serum *HIF-1α* levels between TNBC and luminal BC patients (p = 0.04). The mean ± SD *HIF-1α* levels were 0.39 ± 0.94 in TNBC and 0.14 ± 0.65 in luminal BC patients. Median (IQR) values were 0 (0–0.137) in TNBC and 0 (0–0) in luminal BC patients. The results are summarized in Table 3.

In contrast, Ki-67 expression was significantly higher in TNBC compared to luminal BC patients (independent samples Student's t-test, p = 0.02). Mean Ki-67 levels were 35.77 ± 22.19 in TNBC versus 20.89 ± 13.69 in luminal BC patients (Table 3).

Correlation Analysis

Correlation analysis of serum *IL-6* and *HIF-1α* levels with pathological parameters showed a significant positive correlation between *HIF-1α* and SBR grade in the TNBC subgroup (n = 21, Spearman's rho = 0.57, p = 0.02). No significant correlations were observed between *IL-6* or *HIF-1α* and the other clinicopathological parameters (Table 4).

Discussion

Breast cancer (BC) remains the most prevalent malignancy among women worldwide. It is clinically classified into four surrogate subtypes with distinct biological behaviors: Luminal A-like, Luminal B-like (HER2-negative or HER2-positive), HER2-positive

Table 3. ComparativeAnalysis of *IL-6* and *HIF-1α* Serum Levels between TN and Luminal BC Patients

Marker	Group	n	Mean ± SD	Median (IQR)	Test	p-value
IL-6	TNBC	21	228.22 ± 490.07	8.62 (0–186.46)	Mann–Whitney U	0.21
	Luminal BC	39	78.08 ± 179.04	0 (0–115.69)		
HIF-1α	TNBC	21	0.39 ± 0.94	0 (0–0.137)	Mann–Whitney U	0.04
	Luminal BC	39	0.14 ± 0.65	0 (0–0)		
Ki-67	TNBC	21	35.77 ± 22.19	—	Student's t-test	0.02
	Luminal BC	39	20.89 ± 13.69	—		

Table 4. Correlation analysis of patients serum of IL-6 and Hif 1 with pathological parameters

Parameters	Tumor size	SBR grade	Ki-67
IL-6			
TNBC p-value (Spearman's rho)	0.55 (0.14)	0.8 (0.058)	0.5 (0.24)
Luminal p-value (Spearman's rho)	0.57 (-0.09)	0.18 (0.22)	0.68 (0.07)
HIF-1α			
TNBC p-value (Spearman's rho)	0.43 (-0.18)	0.02 (0.57)	0.84 (0.09)
Luminal p-value (Spearman's rho)	0.12 (0.24)	0.88 (0.024)	0.28 (-0.19)

(non-luminal), and TNBC [10]. Although Luminal BC represents the majority of cases and generally carries a favorable prognosis, its inherent heterogeneity complicates patient stratification and the identification of those at high risk for metastatic relapse [11]. Similarly, TNBC is characterized by significant heterogeneity, encompassing diverse molecular subtypes such as basal-like, immunomodulatory, luminal androgen receptor, mesenchymal, and claudin-low [12].

The clinicopathological distribution observed in our cohort is consistent with established literature, confirming that our study population reflects the standard clinical presentation of these molecular subtypes. Specifically, the predominance of SBR grade 2 and tumor size T2 in our Luminal group aligns with the findings of Molière et al. [13], and Colleoni et al. [14]. Similarly, the histological profile and the prevalence of T2 staging in our TNBC subgroup corroborate previous reports by Jung et al. [15], Kwon et al. [16] and Humbert et al. [17]. These correlations provide a reliable baseline for the subsequent evaluation of circulating biomarkers and their potential association with tumor aggressiveness.

Regarding histological characteristics, TNBC is predominantly composed of NST, though other rare variants such as medullary, metaplastic, and adenoid cystic carcinomas are also reported [4, 18]. Similarly, Caldarella et al. [19] identified NST as the most frequent histological type among Luminal subtypes. Our findings align with these established data, as the NST histotype was the most prevalent in both our Luminal and TNBC cohorts, further validating the representativeness of our study population [4, 18, 19].

Hypoxia is a pivotal driver of malignancy, orchestrating complex cellular responses such as neovascularization and metastasis. These processes are primarily mediated by Hypoxia-Inducible Factors (HIFs), a family of transcription factors that regulate the expression of genes essential for metabolic adaptation to oxygen-deprived environments. By activating pathways involved in epithelial-mesenchymal transition and angiogenesis, HIFs significantly contribute to the aggressive phenotype and metastatic potential observed in various cancers, including the BC subtypes evaluated in this study [20]. *HIF-1α* is a key transcription factor in carcinogenesis and metastatic propagation [7]. In BC, cells respond to hypoxia by activating *HIF-1α*, regulating numerous genes involved in metastatic progression. TNBC is recognized as a highly aggressive and hypoxic subtype compared to other BC subtypes [6]. In TNBC tissue, the positive expression rate of *HIF-1α* was reported at 86.7%, significantly higher than in adjacent tissues or other molecular types, and correlated with histological grade [21]. This pronounced hypoxic signature in TNBC is further supported by several studies [22-24]. Specifically, Badowska-Kozakiewicz et al. [24] revealed strong *HIF-1α* expression in TNBC, while in vitro data from Wang et al. showed that TNBC cell lines (e.g., MDA-MB-231) exhibit the strongest basal expression even under normoxia [25]. Clinically, TNBC is characterized by rapid growth and progression, indicating that *HIF-1α* plays a major role in its malignant biological behavior [25]. Furthermore, high *HIF-1α* expression has been linked to BRCA1 mutations and the basal-like phenotype [2, 26, 27]. Given that TNBC has limited therapeutic options, inhibiting *HIF-1α* (e.g., with YC-1) has been shown to suppress growth and angiogenesis [28, 29]. Recently, Han et al. demonstrated that *HIF-1α* is hyperactivated in MDA-MB-231 cells, regulating genes essential for survival, invasion, and metabolism, which reinforces the HIF pathway as a promising therapeutic target in TNBC [30].

In our study, we identified a significant difference in serum *HIF-1α* concentrations between TNBC and Luminal BC patients, with higher levels observed in the TN group. These findings confirm previous literature stating that TNBC exhibits a more pronounced expression of *HIF-1α* compared to Luminal types [6, 21].

Regarding clinico-pathological parameters, several studies have reported no association between *HIF-1α* and Ki-67 or tumor size in both TNBC and Luminal subtypes [21, 31, 32]. This is further supported by research indicating a lack of correlation between *HIF-1α* and tumor size across all histological types of BC [23]. Our data are in full accordance with these findings, suggesting that circulating *HIF-1α* levels may be independent of tumor volume and proliferative indices in these molecular subtypes.

However, a significant positive correlation was found between *HIF-1α* and SBR grade in TNBC. This aligns with recent studies investigating the potential mechanisms of *HIF-1α* in TNBC development [21], as well as findings by Yan et al. linking *HIF-1α* to high tumor grade [33]. Given that a high percentage of TNBC cases (66.7%) are classified as SBR grade 3 compared to only 30.8% in other BC groups [34], this relationship underscores the role of hypoxia in high-grade malignancy. Similar correlations between *HIF-1α* and histopathological grades have also been documented in other cancers, such as oral squamous cell carcinoma [35]. While our results are in keeping with these studies, more in-depth research is required to fully elucidate the molecular mechanisms linking hypoxia to histological dedifferentiation in TNBC.

Regarding *IL-6*, this pleiotropic cytokine plays a critical role in immune response and inflammation. Its direct effect on BC cell growth remains complex and slightly contradictory; while some studies suggest growth-inhibitory effects, others point toward growth-promoting properties [7]. Mechanistically, STING-mediated NF-κB activation has been shown to induce *IL-6* expression in TNBC cells, activating pSTAT3 and enhancing cell survival and PD-L1 expression [36].

While the basal-like subtype (associated with a TN profile) has been reported to exhibit higher serum *IL-6* levels than other subtypes [9, 37], our study found no significant difference in serum *IL-6* concentrations across the various BC molecular types. This observation is consistent with our previous work [7].

Although Vecchi et al. [9] and Pe et al. [37] demonstrated significantly higher *IL-6* expression in TNBC tissue compared to non-TNBC or Luminal subtypes, the lack of statistical significance in our serum-based analysis warrants careful interpretation. This discrepancy may suggest that systemic (serum) levels do not always mirror local tumor microenvironment expression. Furthermore, it is possible that our study was underpowered to detect these subtle variations in circulating cytokine levels. These findings highlight the complexity of using *IL-6* as a systemic biomarker and underscore the need for larger cohort studies to clarify its diagnostic utility across different BC subtypes.

While the basal-like type (associated with a TN profile) has been reported to have higher serum *IL-6* levels than other subtypes [9, 37], our study found no significant difference in serum *IL-6* concentrations across the different BC molecular types. This observation is consistent with our previous work [7]. Although Vecchi et al. [9] and Pe et al. [37] demonstrated higher *IL-6* expression in TNBC tissue compared to non-TNBC or Luminal subtypes, the lack of significance in our serum-based analysis may suggest that systemic levels do not always mirror local tissue expression, or that the study was underpowered to detect these subtle variations.

In the present study, serum *IL-6* concentrations were higher in TNBC than in Luminal types, though the difference did not reach statistical significance. More detailed studies on larger cohorts are required to fully understand the expression profile and mechanisms of *IL-6* within each molecular group.

Regarding clinico-pathological correlations, a meta-analysis by Lin et al. [38] showed that *IL-6* expression in BC does not correlate with tumor size or histological grade. Similarly, a study conducted at the National Centre Hospital in Korea found no association between serum *IL-6* levels and SBR grade or tumor size [39]. Our results are in line with these previous reports, confirming that *IL-6* is not associated with SBR grade or tumor size in either TNBC or Luminal BC.

The Ki-67 Labelling Index (LI), a nuclear protein, is a well-established diagnostic and prognostic marker in various malignancies [40]. Recently, the IHC expression of Ki-67 has been investigated as a predictive biomarker for achieving pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) in TNBC patients [41, 42]. Srivastava et al. noted that TNBCs frequently exhibit a high Ki-67 proliferation index and respond favorably to NAC, achieving pCR in approximately 40% of cases [43]. Our results demonstrate a significant difference in Ki-67 levels between TNBC and Luminal BC, with the TNBC subtype showing significantly higher expression. These findings are in agreement with literature data indicating that the TNBC molecular type is biologically more aggressive than the Luminal type.

Study Limitations

This study has several limitations that should be acknowledged. First, the relatively small sample size, particularly in the TNBC subgroup (n = 21), may have limited the statistical power of the analyses, potentially explaining the lack of significant associations involving *IL-6*. Second, while standardized procedures for sample collection and storage were strictly followed, the assessment of circulating cytokines like *IL-6* can be influenced by biological and pre-analytical variability due to their inherent instability. Consequently, larger multi-center studies with increased sample sizes are warranted to further validate these findings and clarify the clinical utility of these biomarkers.

In conclusion, our results show elevated levels of *HIF-1α* in TNBC compared with luminal subtypes, suggesting that *HIF-1α* may be associated with the aggressive biological behavior of TNBC. We observed a positive association between *HIF-1α* and SBR grade in TNBC, indicating that higher *HIF-1α* levels are associated with increased tumor aggressiveness.

Taken together, these findings suggest that *HIF-1α* may represent a potential biomarker associated with tumor aggressiveness in TNBC. However, given the

exploratory nature of this study and the limited sample size, these results should be interpreted with caution, and further studies using larger, well-characterized cohorts are required to confirm its clinical relevance.

In contrast, *IL-6* expression did not differ significantly between TNBC and luminal breast cancer, and no associations with clinicopathological parameters were observed. These findings suggest that *IL-6* may have a limited role in distinguishing between these subtypes in this cohort, although its role in tumor biology remains to be further elucidated.

Acknowledgements

The authors would like to thank the staff of the Medical Oncology and Gynecology Oncology units at EHU Oran, Algeria, for their support and assistance in patient recruitment and data collection. We also extend our gratitude to the research team at the LBDD laboratory and the Department of Biology at University of Oran 1 Ahmed Ben Bella for their technical support and valuable guidance throughout this study.

Ethical Approval

The study was approved by the Ethical Committee of Batna 2 University (Ref: 2024/R/U.B.2/) in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Data Availability

This study's data is not openly available.

Authors' Disclosures

The authors declare no conflicts of interest related to this study.

Authors' Contributions

SY: Literature search, manuscript preparation, performance of experimental techniques, recruitment of patients, and collection of data from medical records. ZT, AM: Analysis of *IL-6* by ELISA and interpretation of results., biostatistical analysis and assistance with manuscript writing. TS: Laboratory director; supervision of experimental work, guidance on study design, planning of experiments, procurement of kits, and assistance with writing and reviewing the manuscript.

References

1. Perou CM, Sørlie T, Eisen MB, Rijn M, Jeffrey SS, Rees CA, Pollack JR, et al. Molecular portraits of human breast tumours. Nature. 2000 08 17;406(6797):747-752. https://doi.org/10.1038/35021093
2. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proceedings of the National Academy of Sciences of the United States of America. 2001 09 11;98(19):10869-10874. https://doi.org/10.1073/pnas.191367098
3. Darbeheshti F, Izadi P, Razavi ANE, Kamali F, Yekaninejad MS, Bazzaz JT. Significance of EGFR mRNA expression in luminal and triple negative breast tumors. International Journal of Cancer Management. 2018;11(2).
4. Sasaki Y, Tsuda H. Clinicopathological characteristics of triple-negative breast cancers. Breast Cancer. 2009;16(4):254-259. https://doi.org/10.1007/s12282-009-0153-5
5. Byun Y, Choi Y, Jeong Y, Lee G, Yoon S, Jeong Y, Yoon J, Baek K. MiR-200c downregulates *HIF-1α* and inhibits migration of lung cancer cells. Cellular & Molecular Biology Letters. 2019;24:28. https://doi.org/10.1186/s11658-019-0152-2
6. Liu Q, Guan C, Liu C, Li H, Wu J, Sun C. Targeting hypoxia-inducible factor-1alpha: A new strategy for triple-negative breast cancer therapy. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2022 Dec;156:113861. https://doi.org/10.1016/j.biopha.2022.113861
7. Yahia S, Tahari Z, Medjdoub A, Tahari FZ, Bessaih N, Messatfa M, Deblaoui F, et al. Expression profile of interleukin-6, 4-hydroxy-2-nonenal, and hypoxia-inducible factor 1-α in women with breast cancer and their association with clinicopathological parameters. Contemporary Oncology. 2023;27(1):14-21. https://doi.org/10.5114/wo.2023.127199
8. Ahmad N, Ammar A, Storr SJ, Green AR, Rakha E, Ellis IO, Martin SG. *IL-6* and IL-10 are associated with good prognosis in early stage invasive breast cancer patients. Cancer immunology, immunotherapy: CII. 2018 04;67(4):537-549. https://doi.org/10.1007/s00262-017-2106-8
9. Vecchi L, Mota STS, Zóia MAP, Martins IC, Souza JB, Santos TG, Beserra ADO, et al. Interleukin-6 Signaling in Triple Negative Breast Cancer Cells Elicits the Annexin A1/Formyl Peptide Receptor 1 Axis and Affects the Tumor Microenvironment. Cells. 2022 05 20;11(10):1705. https://doi.org/10.3390/cells11101705
10. López C, Gibert-Ramos A, Bosch R, Korzynska A, García-Rojo M, Bueno G, García-Fontgivell JF, et al. Differences in the Immune Response of the Nonmetastatic Axillary Lymph Nodes between Triple-Negative and Luminal A Breast Cancer Surrogate Subtypes. The American Journal of Pathology. 2021 03;191(3):545-554. https://doi.org/10.1016/j.ajpath.2020.11.008
11. Tabor S, Szostakowska-Rodzos M, Fabisiewicz A, Grzybowska EA. How to Predict Metastasis in Luminal Breast Cancer? Current Solutions and Future Prospects. International Journal of Molecular Sciences. 2020 Nov 09;21(21):8415. https://doi.org/10.3390/ijms21218415
12. Surveillance E, Program ER. SEER Cancer Statistics Review (CSR) 1975-2018. 2021.
13. Molière S, Lodi M, Leblanc S, Gressel A, Mathelin C, Alpy F, Chenard M, Tomasetto C. MMP-11 expression in early luminal breast cancer: associations with clinical, MRI, pathological characteristics, and disease-free survival. BMC cancer. 2024 03 04;24(1):295. https://doi.org/10.1186/s12885-024-11998-0
14. Colleoni M, Rotmensz N, Maisonneuve P, Mastropasqua MG, Luini A, Veronesi P, Intra M, et al. Outcome of special types of luminal breast cancer. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2012 06;23(6):1428-1436. https://doi.org/10.1093/annonc/mdr461
15. Jung S, Kim HY, Nam B, Min SY, Lee SJ, Park C, Kwon Y, et al. Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer. Breast Cancer Research and Treatment. 2010 04;120(3):627-637. https://doi.org/10.1007/s10549-010-0780-8
16. Kwon J, Eom K, Koo TR, Kim BH, Kang E, Kim S, Kim YJ, Park SY, Kim IA. A Prognostic Model for Patients with Triple-Negative Breast Cancer: Importance of the Modified Nottingham Prognostic Index and Age. Journal of Breast Cancer. 2017 03;20(1):65-73. https://doi.org/10.4048/

jbc.2017.20.1.65
17. Humbert O, Riedinger J, Charon-Barra C, Berriolo-Riedinger A, Desmoulins I, Lorgis V, Kanoun S, et al. Identification of Biomarkers Including 18FDG-PET/CT for Early Prediction of Response to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research. 2015 Dec 15;21(24):5460-5468. https://doi.org/10.1158/1078-0432.CCR-15-0384
18. Ishikawa Y, Horiguchi J, Toya H, Nakajima H, Hayashi M, Tagaya N, Takeyoshi I, Oyama T. Triple-negative breast cancer: histological subtypes and immunohistochemical and clinicopathological features. Cancer Science. 2011 03;102(3):656-662. https://doi.org/10.1111/j.1349-7006.2011.01858.x
19. Caldarella A, Buzzoni C, Crocetti E, Bianchi S, Vezzosi V, Apicella P, Biancalani M, et al. Invasive breast cancer: a significant correlation between histological types and molecular subgroups. Journal of Cancer Research and Clinical Oncology. 2013 04;139(4):617-623. https://doi.org/10.1007/s00432-012-1365-1
20. Darbeheshti F, Mahdiannasser M, Noroozi Z, Firoozi Z, Mansoori B, Daraei A, Bastami M, et al. Circular RNA-associated ceRNA network involved in HIF-1 signalling in triple-negative breast cancer: circ_0047303 as a potential key regulator. Journal of Cellular and Molecular Medicine. 2021 Dec;25(24):11322-11332. https://doi.org/10.1111/jcmm.17066
21. Chen M, Liu Z, Zheng K, Hu C, Peng P. The potential mechanism of *HIF-1α* and CD147 in the development of triple-negative breast cancer. Medicine. 2024 06 07;103(23):e38434. https://doi.org/10.1097/MD.0000000000038434
22. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012 Oct 04;490(7418):61-70. https://doi.org/10.1038/nature11412
23. Tutzauer J, Sjöström M, Holmberg E, Karlsson P, Killander F, Leeb-Lundberg LMF, Malmström P, et al. Breast cancer hypoxia in relation to prognosis and benefit from radiotherapy after breast-conserving surgery in a large, randomised trial with long-term follow-up. British Journal of Cancer. 2022 05;126(8):1145-1156. https://doi.org/10.1038/s41416-021-01630-4
24. Badowska-Kozakiewicz AM, Budzik MP. Triple-negative breast cancer: expression of hypoxia-inducible factor 1α in triple-negative breast cancer with metastasis to lymph nodes. Breast Cancer and Surgery. 2018..
25. Wang F, Chang M, Shi Y, Jiang L, Zhao J, Hai L, Sharen G, Du H. Down-regulation of hypoxia-inducible factor-1 suppresses malignant biological behavior of triple-negative breast cancer cells. International Journal of Clinical and Experimental Medicine. 2014;7(11):3933-3940.
26. Turner NC, Reis-Filho JS. Basal-like breast cancer and the BRCA1 phenotype. Oncogene. 2006 09 25;25(43):5846-5853. https://doi.org/10.1038/sj.onc.1209876
27. Groep P, Bouter A, Menko FH, Wall E, Diest PJ. High frequency of HIF-1alpha overexpression in BRCA1 related breast cancer. Breast Cancer Research and Treatment. 2008 Oct;111(3):475-480. https://doi.org/10.1007/s10549-007-9817-z
28. Li Y, Zhang M, Zhang S, Sun X, Zhou C, Li J, Liu J, et al. *HIF-1α* inhibitor YC-1 suppresses triple-negative breast cancer growth and angiogenesis by targeting PlGF/VEGFR1-induced macrophage polarization. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2023 05;161:114423. https://doi.org/10.1016/j.biopha.2023.114423
29. Han D, Li Z, Luo L, Jiang H. Targeting Hypoxia and HIF1α in Triple-Negative Breast Cancer: New Insights from Gene Expression Profiling and Implications for Therapy. Biology. 2024 07 31;13(8):577. https://doi.org/10.3390/biology13080577
30. Rajković-Molek K, Mustać E, Hadžisejdić I, Jonjić N. The prognostic importance of nuclear factor κB and hypoxia-inducible factor 1α in relation to the breast cancer subtype and the overall survival. Applied immunohistochemistry & molecular morphology: AIMM. 2014 07;22(6):464-470. https://doi.org/10.1097/PAI.0b013e31829271ce
31. Campbell EJ, Dachs GU, Morrin HR, Davey VC, Robinson BA, Vissers MCM. Activation of the hypoxia pathway in breast cancer tissue and patient survival are inversely associated with tumor ascorbate levels. BMC cancer. 2019 04 03;19(1):307. https://doi.org/10.1186/s12885-019-5503-x
32. Yan M, Rayoo M, Takano EA, Fox SB. BRCA1 tumours correlate with a HIF-1alpha phenotype and have a poor prognosis through modulation of hydroxylase enzyme profile expression. British Journal of Cancer. 2009 Oct 06;101(7):1168-1174. https://doi.org/10.1038/sj.bjc.6605287
33. Thangjam N, Marbaniang E, Dey B, Harris C, Lynser D, Kalita P. Immunohistochemical Expression of Hypoxia-Inducible Factor-1 Alpha in Oral Squamous Cell Carcinoma. Cureus.17(5):e84597. https://doi.org/10.7759/cureus.84597
34. Ali MJM, AL-Khafaji HAR, Hassoon AF. Immunohistochemical Expression of Hypoxia-Inducible Factor-1α in Triple Negative Breast Cancer. Medical Journal of Babylon. 2015;12(4):902-15.
35. Youssef HE-SM, Abo-Azma NEE, Megahed EME. Correlation of hypoxia-inducible factor-1 alpha (HIF-1a) and vascular endothelial growth factor (VEGF) expressions with clinico-pathological features of oral squamous cell carcinoma (OSCC)..
36. Vasiyani H, Mane M, Rana K, Shinde A, Roy M, Singh J, Gohel D, et al. DNA damage induces STING mediated *IL-6*-STAT3 survival pathway in triple-negative breast cancer cells and decreased survival of breast cancer patients. Apoptosis: An International Journal on Programmed Cell Death. 2022 Dec;27(11-12):961-978. https://doi.org/10.1007/s10495-022-01763-8
37. Pe KCS, Saetung R, Yodsurang V, Chaotham C, Suppipat K, Chanvorachote P, Tawinwung S. Triple-negative breast cancer influences a mixed M1/M2 macrophage phenotype associated with tumor aggressiveness. PloS One. 2022;17(8):e0273044. https://doi.org/10.1371/journal.pone.0273044
38. Lin S, Gan Z, Han K, Yao Y, Min D. Interleukin-6 as a prognostic marker for breast cancer: a meta-analysis. Tumori. 2015;101(5):535-541. https://doi.org/10.5301/tj.5000357
39. Cho YA, Sung M, Yeon J, Ro J, Kim J. Prognostic role of interleukin-6, interleukin-8, and leptin levels according to breast cancer subtype. Cancer Research and Treatment. 2013 09;45(3):210-219. https://doi.org/10.4143/crt.2013.45.3.210
40. Arafah MA, Ouban A, Ameer OZ, Quek KJ. KI-67 LI Expression in Triple-Negative Breast Cancer Patients and Its Significance. Breast Cancer: Basic and Clinical Research. 2021;15:11782234211016977. https://doi.org/10.1177/11782234211016977
41. Keam B, Im S, Lee K, Han S, Oh D, Kim JH, Lee S, et al. Ki-67 can be used for further classification of triple negative breast cancer into two subtypes with different response and prognosis. Breast cancer research: BCR. 2011 03 02;13(2):R22. https://doi.org/10.1186/bcr2834

42. Li X, Liu M, Zhang Y, Wang J, Zheng Y, Li J, Ma B, Song X. CK5/6, EGFR, Ki-67, cyclin D1, and nm23-H1 protein expressions as predictors of pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer patients. Medical Oncology. 2011 Dec;28 Suppl 1:S129-134. https://doi.org/10.1007/s12032-010-9742-6
43. Srivastava P, Wang T, Clark BZ, Yu J, Fine JL, Villatoro TM, Carter GJ, et al. Clinical-pathologic characteristics and response to neoadjuvant chemotherapy in triple-negative low Ki-67 proliferation (TNLP) breast cancers. NPJ breast cancer. 2022 04 20;8(1):51. https://doi.org/10.1038/s41523-022-00415-z