DOI:10.31557/APJCN.2759.20260531

RESEARCH ARTICLE

The Relationship between Phosphatidyl-inositol-3-kinase (PI3K) and Mammalian target of rapamycin (MTOR) mRNA Expression with Lymphovascular Invasion and Ipsilateral Lymph Node Metastasis in Triple-Negative Operable Breast Cancer

Dian Ibnu Wahid, R. Artanto Wahyono, Kunta Setiaji, Herjuna Hardiyanto, Suwardjo Suwardjo, Sumadi Lukman Anwar, Teguh Aryandono, Irianiwati Irianiwati

Division of Oncology Surgery, Surgery Department, Soeradji Tirtonegoro Hospital, Klaten, Indonesia.

Abstract

Background: Triple Negative Breast Cancer (TNBC) is an aggressive subtype of breast cancer characterized by high proliferation, early metastasis, and poor prognosis. The phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) signaling pathway regulates cell proliferation, migration, and invasion, and may play a role in lymphovascular invasion (LVI) and lymph node metastasis. Understanding its role may provide insight into the metastatic potential of TNBC and identify potential biomarkers for prognosis and therapy. **Objective:** To analyze the relationship between PI3K and mTOR mRNA expression with lymphovascular invasion and ipsilateral axillary lymph node metastasis in operable TNBC patients. **Methods:** This was an observational analytic cross-sectional study using secondary data from operable TNBC patients treated at Dr. Sardjito General Hospital, Yogyakarta. A total of 54 samples met the inclusion criteria. The relationships between PI3K/mTOR expression, LVI, and lymph node metastasis were analyzed using Chi-square and Fisher's exact tests, with $p < 0.05$ considered statistically significant. **Result:** High PI3K expression was observed in 50 patients (92.6%), while high mTOR expression was found in 46 patients (85.2%). Lymphovascular invasion was positive in 48 patients (88.9%), and ipsilateral lymph node metastasis occurred in 41 patients (75.9%). High PI3K expression showed a significant association with LVI ($p = 0.010$) and lymph node metastasis ($p = 0.013$). Similarly, high mTOR expression was significantly associated with both LVI ($p < 0.001$) and lymph node metastasis ($p < 0.001$). Multicollinearity testing showed no significant interaction between PI3K and mTOR (VIF = 1.298; tolerance = 0.770), indicating independent effects. **Conclusion:** High PI3K and mTOR mRNA expression are significantly associated with lymphovascular invasion and ipsilateral lymph node metastasis in operable TNBC, supporting their role in tumor aggressiveness and metastatic potential. These findings suggest that PI3K and mTOR could serve as prognostic biomarkers and potential therapeutic targets in TNBC management.

Keywords: Triple Negative Breast Cancer- PI3K- mTOR- Lymphovascular Invasion- Lymph Node Metastasis

Asian Pac J Cancer Nursing, 239-244 Submission Date: 02/27/2026 Acceptance Date: 04/05/2026

Introduction

Breast cancer remains a major global health problem, with approximately 2.3 million new cases and 685,000 deaths reported worldwide in 2020, accounting for about 16% of cancer-related mortality among women [1]. Triple-negative breast cancer (TNBC) is an aggressive subtype characterized by rapid tumor growth, high proliferation rates, early metastasis, and poor prognosis. The overall survival of TNBC patients averages 21.8

Corresponding Author:
Dr. Dian Ibnu Wahid
Division of Oncology Surgery, Surgery Department, Soeradji Tirtonegoro Hospital, Klaten, Indonesia.
Email: dianibnu13@gmail.com

months, with a range of 6.0–108.0 months [2, 3]. Lymph node metastasis is a critical determinant of disease stage, prognosis, and metastatic progression in breast cancer patients [4].

The identification of molecular targets is particularly important in TNBC because this subtype lacks hormone receptors and HER2 expression. Among the key pathways involved in TNBC progression is the phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) signaling pathway, which regulates cell proliferation, migration, invasion, and epithelial–mesenchymal transition (EMT) [5-8]. Activation of this pathway also contributes to chemotherapy resistance through increased drug efflux mediated by ATP-binding cassette (ABC) transporters [9, 10].

However, evidence regarding the association between PI3K and mTOR expression, lymphovascular invasion, and axillary lymph node metastasis in TNBC remains limited. Therefore, this study aimed to evaluate the relationship between PI3K and mTOR mRNA expression and ipsilateral lymph node metastasis in TNBC patients and to explore their potential role as prognostic biomarkers.

Methods

Study Design and Participants

This observational analytic study used a cross-sectional design based on secondary data from medical records of triple-negative breast cancer (TNBC) patients who underwent surgery at Dr. Sardjito General Hospital, Yogyakarta. Data were collected from January 1, 2018, to June 1, 2024, or until the required sample size was reached. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine and Public Health, Universitas Gadjah Mada.

The study population consisted of patients with operable TNBC stages I–IIIB who underwent surgery and immunohistochemical examination between January 1, 2018, and May 31, 2022. The minimum sample size was calculated using the two-proportion hypothesis formula, resulting in at least 47 subjects.

Inclusion criteria were female patients with histopathologically confirmed operable TNBC, no history of neoadjuvant chemotherapy, available pathological specimens suitable for PI3K and mTOR mRNA examination, and complete records of ipsilateral lymph node metastasis. Patients with non-TNBC breast cancer, prior neoadjuvant therapy, other malignancies, incomplete clinical data, or conditions affecting PI3K/mTOR expression were excluded.

Data Collection and Analysis

The independent variables were PI3K and mTOR mRNA expression, while the dependent variable was ipsilateral axillary lymph node metastasis. Tumor specimens from paraffin blocks obtained during radical mastectomy with axillary lymph node dissection were analyzed using quantitative real-time polymerase chain reaction (qRT-PCR). Lymphovascular invasion (LVI) data were obtained from histopathological reports.

Descriptive statistics were presented as frequencies and percentages. Associations between gene expression and metastatic outcomes were analyzed using Chi-square or Fisher's exact tests. Multicollinearity analysis was performed to assess interactions between independent variables.

Results

Characteristics of Study Subjects

A total of 62 TNBC cases were initially identified between 2018 and 2022, of which 54 met the inclusion criteria and were included in the analysis. The highest number of diagnoses occurred in 2019 (18 patients), while the lowest numbers were observed in 2020 and 2021 (8 patients each). Most patients were aged 40–60 years (75.8%), with the largest proportion in the 50–60 year group (40.3%), followed by the 40–50 year group (35.5%). The left breast was slightly more frequently affected than the right.

Histopathological findings indicated highly aggressive tumor characteristics. Invasive ductal carcinoma (IDC)

Table 1. Characteristics of Study Subjects

Characteristics	Frequency	Percentage (%)
Years (First Diagnosed)		
2018	16	29.6
2019	18	33.3
2020	8	14.8
2021	8	14.8
2022	4	7.4
Age		
30-40 years	4	7.4
40-50 years	18	33.3
50-60 years	21	38.9
60-70 years	10	18.5
70-80 years	1	1.9
Affected Side of the Breast		
Right	25	46.3
Left	29	53.7
Pathology Type		
ILC	52	96.3
ILC.	1	1.9
Mixed IDC + Mucinous	1	1.9
Pathology Grading		
Grade 2	5	9.3
Grade 3	49	90.7
Primary Tumor		
T1	1	1.9
T2	12	22.2
T3	41	75.9
Ki67		
<20%	2	3.7
>20%	52	96.3

Table 2. Characteristics of mTOR and PI3K

Characteristics	mTOR	%	PI3K
High	46	85.2	50
Low	8	14.8	4
Total	54	100	54

Table 3. Characteristics of LVI Results and Node Metastasis

Characteristics	LVI	%	Metastasis KGB	%
Positive	48	88.9	41	75.9
Negative	6	11.1	13	24.1
Total	54	100	54	100

was the predominant subtype (96.3%). Most tumors were classified as Grade 3 (90.7%), indicating poor differentiation and high proliferative activity. Tumor size was generally large, with T3 tumors observed in 75.9% of patients and T2 tumors in 22.2%. The proliferation index was also high, with Ki-67 >20% detected in 96.3% of cases (Table 1).

PI3K and mTOR Expression

Among the 54 analyzed samples, high PI3K expression was observed in 50 patients (92.6%), while low expression was found in 4 patients (7.4%). High mTOR expression was detected in 46 patients (85.2%), and low expression in 8 patients (14.8%), indicating predominant activation of the PI3K/mTOR signaling pathway in this cohort (Table 2).

Lymphovascular Invasion and Lymph Node Metastasis

Lymphovascular invasion (LVI) was present in 48 patients (88.9%), while 6 patients (11.1%) showed no LVI. Ipsilateral axillary lymph node metastasis was identified in 41 patients (75.9%), whereas 13 patients (24.1%) had no nodal involvement (Table 3).

Association of PI3K Expression with LVI and Lymph Node Metastasis

High PI3K expression was strongly associated with LVI and lymph node metastasis. Among the 50 patients with high PI3K expression, 48 were LVI-positive and 39 had positive lymph node metastasis. In contrast, none of the patients with low PI3K expression showed LVI, although one patient still had lymph node metastasis (Table 4).

Table 4. Characteristics of PI3K Against LVI and Lymph Node Metastasis

	LVI	Total (%)	Lymph Node Metastasis	Total (%)
High PI3K	Positive	48 (88.9)	Positive	39 (72.2)
	Negative	2 (3.7)	Negative	11 (20.4)
Low PI3K	Positive	0 (0)	Positive	1 (1.9)
	Negative	4 (7.4)	Negative	3 (5.6)

Table 5. Chi-Square Test Results for PI3K and LVI

Variable	LVI		p-value
	X^2	df	
PI3K	34.56	1	0.001>

Table 6. Chi-Square Test Results for PI3K and Ipsilateral Axillary Lymph Node Metastasis

Variable	Ipsilateral Axillary Lymph Node Metastasis		p-value
	X2	df	
PI3K	6.129	1	0.039

Chi-square analysis demonstrated a significant association between PI3K expression and LVI ($p = 0.010$). A significant relationship was also observed between PI3K expression and ipsilateral axillary lymph node metastasis ($p = 0.013$), which was confirmed by Fisher's exact test ($p = 0.039$) (Tables 5, 6).

Association of mTOR Expression with LVI and Lymph Node Metastasis

High mTOR expression was also strongly associated with metastatic features. Among patients with high mTOR expression, 43 had positive LVI and 41 had lymph node metastasis. In contrast, although five patients with low mTOR expression showed LVI, none had lymph node metastasis (Table 7).

Statistical analysis revealed a highly significant association between mTOR expression and LVI ($p < 0.001$). Similarly, a strong relationship was found between mTOR expression and ipsilateral axillary lymph node metastasis (Pearson Chi-square = 29.619; $p < 0.001$), confirmed by Fisher's exact test ($p < 0.001$) (Tables 8, 9).

Multicolinearity Analysis

Multicollinearity testing demonstrated a tolerance value of 0.770 and a variance inflation factor (VIF) of 1.298, indicating no significant multicollinearity between PI3K and mTOR. These results suggest that both variables independently contribute to lymphovascular invasion and lymph node metastasis (Table 10).

Discussion

This study included 54 patients with triple-negative breast cancer (TNBC) diagnosed between 2018 and 2022. The annual distribution of cases varied, with the highest number in 2019 and fewer cases in subsequent years. The relatively small number of TNBC cases each year reflects the lower incidence of this subtype compared with other breast cancer types. Globally, TNBC accounts for approximately 12–13% of breast cancer cases in Western countries, with higher prevalence reported in certain populations, such as Black women (22–24%) and in some Asian populations, including India, where the prevalence may reach 31% [11]. Thus, the limited number of eligible cases in this study likely reflects the epidemiological characteristics of TNBC itself.

Table 7. Characteristics of mTOR in Relation to LVI and Lymph Node Metastasi

	LVI	Total (%)	Lymph Node Metastasis	Total (%)
High mTOR	Positive	43 (79.6)	Positive	41 (75.9)
	Negative	3 (5.6)	Negative	5 (9.3)
Low mTOR	Positive	5 (9.3)	Positive	0 (0)
	Negative	3 (5.6)	Negative	8 (14.8)

Most patients in this study were middle-aged to older adults, with the highest prevalence in the 50–60 year age group. This distribution is consistent with previous epidemiological studies indicating that TNBC frequently occurs in women older than 50 years. Carey et al. reported that TNBC is commonly diagnosed in women younger than 40 years and older than 50 years, with a higher peak incidence in older age groups compared with other breast cancer subtypes [12]. Similarly, Yuan et al. found that TNBC prevalence increases among women over 50 years of age [13].

Breast cancer in this cohort was slightly more common in the left breast than the right. This finding is consistent with previous epidemiological studies demonstrating a higher incidence of breast cancer in the left breast. Zheng et al. reported that left-sided breast cancer occurs more frequently across multiple populations [14]. One possible explanation is anatomical differences between the breasts, as the left breast typically contains a larger volume of glandular tissue, which may increase susceptibility to tumor development [15].

Histopathological analysis revealed that invasive ductal carcinoma (IDC) was the predominant subtype, accounting for 96.3% of cases. This finding aligns with global data indicating that IDC represents approximately 70–80% of all breast cancers. The predominance of IDC is attributed to its origin in ductal epithelial cells, which are the most common site of malignant transformation. Only a small number of rare histological subtypes were identified, consistent with their lower prevalence in breast cancer populations [16].

Most tumors in this study were classified as grade 3, reflecting the aggressive biological characteristics of TNBC. High-grade tumors are associated with poor differentiation and increased proliferative activity. Previous studies have reported that TNBC is frequently characterized by high-grade histology and aggressive tumor behavior [17]. The predominance of grade 3 tumors in this cohort may also reflect delayed diagnosis, as many patients in Indonesia present at advanced stages due to limited screening access and lower public awareness. Similar findings were reported by Gondhowiardjo et al., who highlighted the association between delayed diagnosis and poorer cancer outcomes in Indonesia [18].

Consistent with the aggressive nature of TNBC, most tumors in this study were large, with the majority classified as T3. Large tumor size at diagnosis is commonly reported in TNBC and is often associated with delayed detection. Factors such as limited screening programs, socioeconomic barriers, and lack of awareness may contribute to later-stage presentation. Similar observations were reported by Eastman et al., who found that delayed treatment in TNBC is associated with larger tumor size and poorer prognosis [19].

The proliferation index measured by Ki-67 was also markedly elevated in this cohort, with most patients demonstrating Ki-67 levels greater than 20%. Ki-67 is a widely used marker of cellular proliferation, and high Ki-67 expression is strongly associated with aggressive tumor biology and poor prognosis in breast cancer [20]. Molecular classification studies by Perou et al. identified the basal-like subtype closely associated with TNBC as having the highest proliferative activity among breast cancer subtypes [21]. Bhargava et al. further demonstrated that Ki-67 expression is significantly higher in TNBC compared with luminal subtypes, supporting the aggressive proliferative nature of this disease [22].

This study also demonstrated a high prevalence of PI3K expression, which was significantly associated with metastatic features. The PI3K/Akt/mTOR signaling pathway is among the most frequently activated pathways in cancer and plays a critical role in regulating tumor growth, proliferation, and invasion [23]. In this study, high PI3K expression was strongly associated with lymphovascular invasion (LVI), suggesting that PI3K activation contributes to tumor cell migration and invasion into lymphatic vessels.

Mechanistically, PI3K activation promotes cytoskeletal remodeling and enhances cell motility, enabling tumor cells to penetrate surrounding tissues and enter lymphatic or vascular structures [24]. Furthermore, high PI3K expression was also strongly associated with axillary lymph node metastasis, supporting previous reports that activation of the PI3K/Akt/mTOR pathway is associated with increased metastatic potential and poorer clinical outcomes [23].

As an upstream regulator in this signaling cascade, PI3K initiates cellular processes that facilitate tumor invasion and metastatic spread. In the context of LVI, PI3K enhances cancer cell motility through actin

Table 8. Chi-Square Test Results for mTOR with LVI

Variable	LVI		p-value
	X^2	df	
mTOR	6.622	1	0.036

Table 9. Results of the mTOR Chi-Square Test with Ipsilateral Axillary Lymph Node Metastasis

Variable	Ipsilateral Axillary Lymph Node Metastasis		p-value
	X2	df	
mTOR	29.619	1	<0.001

Table 10. Results of the Multicollinearity Test between PI3K and mTOR

Variable	PI3K		p-value
	B	t	
mTOR	0.063	0.311	0.757

cytoskeleton remodeling, allowing tumor cells to infiltrate lymphatic and blood vessels. Increased PI3K expression has been consistently associated with positive LVI and lymph node metastasis in breast cancer [25, 26].

In addition to PI3K, this study found that mTOR expression was also highly prevalent and strongly associated with metastatic features. As a downstream effector of the PI3K/Akt/mTOR pathway, mTOR regulates protein synthesis, cell growth, and metabolic adaptation. High mTOR expression was significantly associated with both lymphovascular invasion and axillary lymph node metastasis, supporting its role in tumor progression. mTOR activation enhances tumor cell survival, facilitates interaction with the extracellular matrix, and enables cancer cells to withstand metabolic stress during metastatic dissemination.

Although PI3K and mTOR are components of the same signaling pathway, they play distinct yet complementary roles in the metastatic process. PI3K primarily promotes tumor invasion by enhancing cellular motility, whereas mTOR supports metastatic colonization by maintaining cellular survival and metabolic stability. Overall, the PI3K/Akt/mTOR pathway functions as an integrated system regulating multiple stages of cancer metastasis, from local invasion to colonization of secondary organs. Activation of this pathway enhances tumor cell motility, promotes lymphovascular invasion, and increases metastatic cell survival through metabolic regulation and suppression of apoptosis. Within the framework of the "seed and soil" hypothesis, activation of this pathway strengthens the tumor "seed" while simultaneously modifying the microenvironment to facilitate metastatic colonization.

From a clinical perspective, the PI3K/Akt/mTOR pathway represents an important therapeutic target in TNBC. Because TNBC lacks hormone receptors and HER2 expression, targeted treatment options remain limited. Overactivation of this pathway contributes to tumor proliferation, invasion, and resistance to chemotherapy. Consequently, inhibitors targeting PI3K, AKT, or mTOR have emerged as potential strategies for improving treatment outcomes in TNBC.

This study has several limitations. The relatively small sample size may limit the generalizability of the findings. In addition, the retrospective design relying on secondary data may introduce potential bias related to incomplete clinical information. Furthermore, this study assessed mRNA expression without evaluating protein expression or pathway activation status. Finally, survival outcomes were not analyzed, preventing assessment of the long-term prognostic impact of PI3K and mTOR expression.

Future studies involving larger cohorts, prospective designs, and integrated molecular analyses are needed to further clarify the role of the PI3K/Akt/mTOR pathway in TNBC progression and to evaluate its potential as a therapeutic target.

In conclussion, this study demonstrates a significant association between PI3K and mTOR mRNA expression and lymphovascular invasion as well as axillary lymph node metastasis in TNBC, highlighting the important role of the PI3K/mTOR pathway in tumor aggressiveness. Although part of the same signaling pathway, PI3K and mTOR act independently, suggesting their potential as prognostic biomarkers. Future studies with prospective designs, larger sample sizes, complete follow-up data, and protein expression analysis (p-PI3K and p-mTOR) using immunohistochemistry are needed to validate these findings and evaluate the effectiveness of targeted therapies.

Author Contribution Statement

All authors contributed equally in this study

Acknowledgements

None

References

1. Benitez Fuentes JD, Morgan E, Luna Aguilar A, Mafra A, Shah R, Giusti F, Vignat J, et al. Global Stage Distribution of Breast Cancer at Diagnosis: A Systematic Review and Meta-Analysis. JAMA oncology. 2024 01 01;10(1):71-78. https://doi.org/10.1001/jamaoncol.2023.4837
2. Baranova A, Krasnoselskyi M, Starikov V, Kartashov S, Zhulkevych I, Vlasenko V, Oleshko K, et al. Triple-negative breast cancer: current treatment strategies and factors of negative prognosis. Journal of Medicine and Life. 2022 02;15(2):153-161. https://doi.org/10.25122/jml-2021-0108
3. Courtney D, Davey MG, Moloney BM, Barry MK, Sweeney K, McLaughlin RP, Malone CM, et al. Breast cancer recurrence: factors impacting occurrence and survival. Irish Journal of Medical Science. 2022 Dec;191(6):2501-2510. https://doi.org/10.1007/s11845-022-02926-x
4. Min SK, Lee SK, Woo J, Jung SM, Ryu JM, Yu J, Lee JE, et al. Relation Between Tumor Size and Lymph Node Metastasis According to Subtypes of Breast Cancer. Journal of Breast Cancer. 2021 02;24(1):75-84. https://doi.org/10.4048/jbc.2021.24.e4
5. Costa RLB, Han HS, Gradishar WJ. Targeting the PI3K/AKT/mTOR pathway in triple-negative breast cancer: a review. Breast Cancer Research and Treatment. 2018 06;169(3):397-406. https://doi.org/10.1007/s10549-018-4697-y
6. Zhang H, Jiang R, Zhu J, Sun K, Huang Y, Zhou H, Zheng Y, Wang X. PI3K/AKT/mTOR signaling pathway: an important driver and therapeutic target in triple-negative breast cancer. Breast Cancer. 2024 07;31(4):539-551. https://doi.org/10.1007/s12282-024-01567-5
7. Rozenchan PB, Pasini FS, Roela RA, Katayama MLH, Mundim FGL, Brentani H, Lyra EC, Brentani MM. Specific upregulation of RHOA and RAC1 in cancer-associated fibroblasts found at primary tumor and lymph node metastatic sites in breast cancer. Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine. 2015 Dec;36(12):9589-9597. https://doi.org/10.1007/s13277-015-3727-1
8. Liu B, Xiong J, Liu G, Wu J, Wen L, Zhang Q, Zhang C. High expression of Rac1 is correlated with partial reversed cell polarity and poor prognosis in invasive ductal carcinoma of the breast. Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine. 2017 07;39(7):1010428317710908. https://doi.org/10.1177/1010428317710908
9. Khan MA, Jain VK, Rizwanullah M, Ahmad J, Jain K. PI3K/AKT/mTOR pathway inhibitors in triple-negative breast

cancer: a review on drug discovery and future challenges. Drug Discovery Today. 2019 Nov;24(11):2181-2191. https://doi.org/10.1016/j.drudis.2019.09.001
10. Dong C, Wu J, Chen Y, Nie J, Chen C. Activation of PI3K/AKT/mTOR Pathway Causes Drug Resistance in Breast Cancer. Frontiers in Pharmacology. 2021;12:628690. https://doi.org/10.3389/fphar.2021.628690
11. Kulkarni A, Kelkar DA, Parikh N, Shashidhara LS, Koppiker CB, Kulkarni M. Meta-Analysis of Prevalence of Triple-Negative Breast Cancer and Its Clinical Features at Incidence in Indian Patients With Breast Cancer. JCO Global Oncology. 2020 Nov;(6):1052-1062. https://doi.org/10.1200/GO.20.00054
12. Anders CK, Carey LA. Biology, Metastatic Patterns, and Treatment of Patients with Triple-Negative Breast Cancer. Clinical Breast Cancer. 2009 06;9:S73-S81. https://doi.org/10.3816/CBC.2009.s.008
13. Yuan N, Meng M, Liu C, Feng L, Hou L, Ning Q, Xin G, et al. Clinical characteristics and prognostic analysis of triple-negative breast cancer patients. Molecular and Clinical Oncology. 2014 03;2(2):245-251. https://doi.org/10.3892/mco.2013.230
14. Zheng X, Xu C, Ganesan K, Chen H, Cheung YS, Chen J. Does Laterality in Breast Cancer still have the Importance to be Studied? A Meta-analysis of Patients with Breast Cancer. Current Medicinal Chemistry. 2024;31(22):3360-3379. https://doi.org/10.2174/0109298673241301231023060322
15. Scutt D, Lancaster GA, Manning JT. Breast asymmetry and predisposition to breast cancer. Breast cancer research: BCR. 2006;8(2):R14. https://doi.org/10.1186/bcr1388
16. Makki J. Diversity of Breast Carcinoma: Histological Subtypes and Clinical Relevance. Clinical medicine insights. Pathology. 2015 Dec 21;8. https://doi.org/10.4137/CPath.S31563
17. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006 06 07;295(21). https://doi.org/10.1001/jama.295.21.2492
18. Hartanto S, Wirawan S, Jayalie VF, Astiti I, Panigoro S, Sekarutami S, Rachman A, Bachtiar A. Treatment delay of cancer patients in Indonesia: a reflection from a national referral hospital. Medical Journal of Indonesia. 2021 06 30;30:129-37. https://doi.org/10.13181/mji.oa.204296
19. Eastman A, Tammaro Y, Moldrem A, Andrews V, Huth J, Euhus D, Leitch M, Rao R. Outcomes of delays in time to treatment in triple negative breast cancer. Annals of Surgical Oncology. 2013 06;20(6):1880-1885. https://doi.org/10.1245/s10434-012-2835-z
20. Wang W, Wu J, Zhang P, Fei X, Zong Y, Chen X, Huang O, et al. Prognostic and predictive value of Ki-67 in triple-negative breast cancer. Oncotarget. 2016 05 24;7(21):31079-31087. https://doi.org/10.18632/oncotarget.9075
21. 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
22. Bhargava R, Striebel J, Beriwal S, Flickinger JC, Onisko A, Ahrendt G, Dabbs DJ. Prevalence, morphologic features and proliferation indices of breast carcinoma molecular classes using immunohistochemical surrogate markers. International Journal of Clinical and Experimental Pathology. 2009;2(5):444-455.
23. Prvanović M, Nedeljković M, Tanić N, Tomić T, Terzić T, Milovanović Z, Maksimović Z, Tanić N. Role of PTEN, PI3K, and mTOR in Triple-Negative Breast Cancer. Life. 2021 Nov 17;11(11):1247. https://doi.org/10.3390/life11111247
24. Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. Nature Reviews. Cancer. 2020 02;20(2):74-88. https://doi.org/10.1038/s41568-019-0216-7
25. Deng S, Leong HC, Datta A, Gopal V, Kumar AP, Yap CT. PI3K/AKT Signaling Tips the Balance of Cytoskeletal Forces for Cancer Progression. Cancers. 2022 03 24;14(7):1652. https://doi.org/10.3390/cancers14071652
26. Ma M, Ma Y, Zhang G, Liao R, Jiang X, Yan X, Bie F, Li X, Lv Y. Eugenol alleviated breast precancerous lesions through HER2/PI3K-AKT pathway-induced cell apoptosis and S-phase arrest. Oncotarget. 2017 08 22;8(34):56296-56310. https://doi.org/10.18632/oncotarget.17626