RESEARCH ARTICLE

INDONESIAN JOURNAL OF CANCER

High Hypoxia Inducible Factor-1α Expression and Positive Limphovascular Invasion as Risk Factors for Axillary Lymph Nodes Metastasis in Breast Cancer

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ARTICLE INFO

Received : 01 September 2024
Revised : 01 November 2024
Accepted : 06 November 2024
Published : 30 June 2025

Keywords:
breast cancer, HIF-1α, lymph node, LVI

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ABSTRACT

Background: Hypoxia-inducible factor-1α (HIF-1α) expression enables tumor cell proliferation and has a role in the processes of epithelial-mesenchymal transition, invasion, extravasation, and metastasis. Lymphovascular Invasion (LVI) causes a significant increase in the occurrence of axilla lymph node metastasis. This study aims to prove that high HIF-1α expression and LVI (+) as risk factors for axillary lymph node metastasis in breast cancer.

Method: The study conducted was a case-control study involving all histopathologically confirmed breast cancer patients at Prof. Dr. I.G.N.G. Ngoerah Hospital during the period from January 2019 to December 2022. In this study, the case group consisted of patients with breast cancer and axilla lymph node (+), while the control group included breast cancer patients without these characteristics. Data analysis was processed using SPSS version 26, which included descriptive statistical analysis, proportion comparison tests, and multiple logistic regression tests, with significance set at $p < 0.05$.

Results: LVI (+) has a risk of metastasis to lymph nodes (+) of 6 times (95% CI 1.53–23.44, P = 0.007) and adjusted OR 4.33 (95% CI 2.369–6.053; P = 0.025). The results of the HIF1-α ROC curve obtained a sensitivity value of 86.4% and specificity of 79.2% with a cut-off value of 5.4. A score ≥ 5.4 has a risk of metastasis to lymph nodes (+) of 24.01 times (95% CI 5.03–115.25; P < 0.001) and adjusted OR 24.06 (95% CI 5.026–115.247; p < 0.001).

Conclusion: High HIF-1α expression and positive lymphovascular invasion as risk factors for axillary lymph node metastasis in breast cancer, with HIF-1α showing a particularly strong association. These findings suggest their potential as predictive biomarkers for metastasis. However, the study's retrospective, single-center design limits generalizability. Future research should validate these results in larger, multicenter cohorts and explore the underlying mechanism to enhance clinical application.

INTRODUCTION

Breast cancer is the most common cancer in women and the biggest cause of death in women, surpassing the death rate from lung cancer [1,2]. Breast cancer metastases can be found at diagnosis (de novo) or in the course of the disease. About 20–30% of breast cancer patients will experience a metastatic episode in the course of their disease. The duration of survival for breast cancer patients with distant metastases is only 24–30 months or less if they have one or more visceral metastases [3]. Metastasis is the leading cause of death in breast cancer patients. Metastasis can occur in 20–30% of all breast cancer patients in the course of their disease [4].

Metastasis to axilla lymph nodes is generally the first site of spread of breast cancer. The behavior of metastatic breast cancer is highly variable and difficult to predict, so the prediction of breast cancer metastasis is very important in clinical practice. Simple and inexpensive markers are needed to predict metastasis so that breast cancer patients who have a high tendency to metastasize receive more aggressive therapeutic modalities. Breast cancer is a disease with high heterogeneity, various factors can play a role in influencing the metastatic process, accompanied by the activation of various signaling pathways, making it difficult to determine the main markers in the cascade of breast cancer invasion and metastasis [5]. Invasion and metastasis is one of the hallmarks of cancer, evolving through a coordinated and highly selective biological process involving multiple mechanisms related to cell proliferation, cellular migration, extracellular-matrix interactions, stromal invasion, evasion of host immune response, and lymphovascular invasion [6]. Distant metastasis involves a complex interaction of the primary tumor environment and systemic factors, including cell proliferation, differentiation, angiogenesis, and the microenvironment [7].

The invasion and metastatic ability of breast cancer cells is highly dependent on the availability of vascularization, tissue angiogenesis, and extracellular matrix material. In the formation of new blood vessels, cancer cells produce several proteins for the angiogenesis process, and one of the most important is vascular endothelial growth factor (VEGF) and its receptors. The role of VEGF is to facilitate this process, and the role of hypoxia inducible factor (HIF) is as a regulator. In hypoxic conditions, cell proliferation does not occur, but will induce HIF to increase metabolic processes, angiogenesis, and cell division [8].

Hypoxic microenvironments play an important role in the regulation of breast cancer progression and metastasis. A key marker of the hypoxic cellular response is Hypoxia inducible factor-1 (HIF-1). This marker is associated with poor prognosis, radioresistance, inhibition of apoptosis, and genomic instability. Cancer cells also have mechanisms to increase HIF-1 protein under normoxia and transcriptional activity, including increased protein translation as a compensatory mechanism under hypoxic conditions [9]. HIF-1α expression enables tumor cell proliferation under hypoxic conditions, both in triggering G1/2 phase replication, angiogenesis, upregulation of metabolic functions, and triggering cancer stem cell development. The role of HIF-1α as a master regulator in breast cancer is involved in the process of epithelial-mesenchymal transition, invasion, extravasation, and metastasis [10].

The spread of cancer cells to local lymph vessels, as well as to blood vessels and indicates that cancer cells have reached both vessels and is Lymphovascular invasion (LVI). Spread that has reached axillary lymph nodules and internal mammary lymph nodules is due to embolization of cancer cells to the nodules, which are formed from a collection of cancer cells. The involved nodules will be enlarged, hard, and pale. The spread of cancer cells to blood vessels will initiate the spread of cancer cells to more distant organs or metastasis [11]. Based on these studies, this study aims to assess HIF-1α and LVI as risk factors for lymph node metastasis in breast cancer patients.

METHODS

The design of this study was a case-control study conducted on breast cancer patients at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali, from January 1, 2019, to December 31, 2022. The study population included cases defined as patients with axillary lymph node-positive breast cancer, confirmed through radiological examinations, and controls defined as breast cancer patients with axillary lymph node-negative status. Exclusion criteria consisted of patients with a history of other malignancies, those with immunosuppressive diseases (such as HIV/AIDS or chronic steroid use), incomplete data, or those who could not be contacted for record completion. Mortality from causes unrelated to breast cancer was also excluded to avoid confounding factors.

The sampling was conducted using a random sampling method, with 46 participants in each group (46 cases and 46 controls), ensuring adequate statistical power to detect associations between axillary lymph node involvement and other variables. Data were analyzed using SPSS version 26 (Windows) in several stages. Descriptive analysis was performed to summarize frequencies, means, and proportions of key demographic and clinical characteristics, such as age, tumor grade, and hormone receptor status. Comparative analysis was conducted by creating 2 x 2 cross-tabulations to calculate the odds ratio (OR), estimating the association between independent variables and axillary lymph node status. A chi-square test was used to determine statistical significance.

Additionally, multivariate analysis was performed using multiple logistic regression to compute the adjusted odds ratio (AOR) and control for potential confounding factors, including age, tumor size, and receptor status. All results were reported with a 95% confidence interval (CI) and p-values, with statistical significance set at $\alpha = 0.05$ ($p < 0.05$). The variables assessed included age, tumor size (T1, T2, T3, T4), tumor grade (low, intermediate, or high), and hormone receptor status (positive/negative for estrogen receptor [ER], progesterone receptor [PR], and HER2). The primary outcome of the study was the association between these independent variables and axillary lymph node involvement.

P-ISSN: 1978-3744 E-ISSN: 2355-6811

RESULTS

In this study, the results of the case group [Axilla lymph nodes Breast Cancer (+)] were 22 subjects, and the control group [Axilla lymph nodes Breast Cancer (-)] was 24 subjects. The data characteristics of the research subjects are presented in **Table 1**.

The results of the HIF-1α score in determining the high and low thresholds used the statistical method Receiver Operating Characteristic (ROC) procedure and assessed the Area Under the Curve (AUC). The results of the ROC curve are presented in **Figure 1**, with the significance results in **Table 2**.

The results of the ROC curve analysis obtained a sensitivity value of 86.4% and a specificity of 79.2% with a cut-off value of 3. Furthermore, based on these values, a risk model for the occurrence of metastasis in the axilla lymph nodes is compiled, which is presented in **Table 3**. The results show that a score ≥ 5.4 has a risk of metastasis in the axilla lymph nodes (+) of 24.01 times (CI 95% 5.03-115.25; P < 0.001).

The association of LVI (+) with the occurrence of metastasis in the lymph nodes is presented in **Table 4**. The results showed that LVI (+) had a risk of metastasis to lymph nodes (+) of 6 times (CI 95% 1.53–23.44, P = 0.007).

The results of logistic regression analysis assessing high HIF-1α and LVI (+) presented in **Table 5** and **Table 6** showed that the factors that play the most role in the dependent variable are high HIF-1α and LVI (+) which are independent variables with the results in high HIF-1α obtained aOR 24.06 (CI 95% 5.026–115.247; p < 0.001) and in LVI (+) obtained aOR 4.33 (CI 95% 2.369–6.053; p = 0.025). The results were significant in

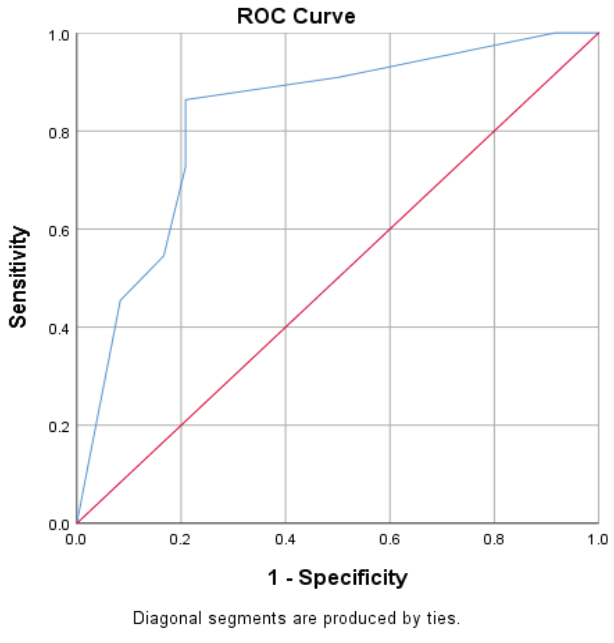

Figure 1. Receiver operating characteristic curve

influencing the risk of axilla lymph nodes metastasis of breast cancer, while other factors such as tumor size, subtype, ER, PR, HER2, Ki67, cell type, and histological grade were not statistically significantly associated with axilla lymph nodes metastasis.

DISCUSSION

The characteristics of the research subjects showed that the age of breast cancer patients was in the 5th decade. This is in accordance with research conducted by Verdial et al. [12] with a mean age of 52.6 ± 8.19 years. The results of this study are in accordance with the characteristics in Bali, namely 65% coming from the age group over 40 years [13,14]. The results of age characteristics at Prof. Dr. IGNG Ngoerah Denpasar Hospital in 2009-2013 from 130 subjects with breast cancer obtained an age group of > 40 years, as many as 77.7% [15]. Data from the American Cancer Society in 2017-2018 found the highest incidence of breast cancer at ages over 40-60 years, namely 68%, with a mortality of 3.4%. While based on data from the World Health obtained, with a median of 63 years [16]. Axillary lymph nodes involvement varies with age at diagnosis; the likelihood decreases with age until approximately 70 years of age, but increases again thereafter. This increase is indeed particularly pronounced in smaller tumors and shows a different behavior than small breast cancers in older adults. It is hypothesized that decreased immune defense mechanisms, associated with aging, may play a role in earlier invasion into the lymph nodes [17].

Breast cancer is a heterogeneous disease at the molecular level, so it can be hypothesized that different molecular subtypes also differ in the tumor microenvironment (TME). Her-2 subtype is rich in M2 tumor-associated macrophages (P = 0.000) compared to triple-negative breast cancer (TNBC) and Luminal B subtypes [18]. The most common breast cancer subtype in the case group [Axilla lymph nodes Breast Cancer (+)] was TNBC. TNBC accounts for 15-25% of all breast cancers [19]. Triple-negative breast cancer is breast cancer that does not express estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [20]. While in the control group [Breast Cancer lymph nodes axilla (-)], the most common subtype is HER2. About 20 percent of breast cancer cases are HER2-positive. HER2-positive breast cancer tends to grow faster and is more likely to spread and return (recur) when compared to HER2-negative breast cancer [21].

Breast cancer subtypes defined by ER, PR, and HER2 status can predict axillary lymph node metastasis in breast cancer. Although TNBC is more aggressive, the risk of axillary lymph nodes metastasis is lower than patients with other subtypes. These findings suggest that lymphatic metastasis is not the main pattern of

Table 1. The data characteristics of the research subjects are presented

Variables	Cases (n = 22) [Axilla lymph nodes Breast Cancer (+)]	Control (n = 24) [Breast Cancer lymph nodes axilla (-)]	P
Age (mean ± SD) years	50.45 ± 11.87	52.50 ± 11.02	0.548
Subtypes			
HER 2	5 (22.7%)	9 (37.5%)	0.132
Luminal A	2 (9.1%)	3 (12.5%)	
Luminal B	3 (13.6%)	7 (29.1%)	
Luminal B (TP)	4 (18.2%)	1 (4.2%)	
TNBC	8 (36.4%)	4 (16.7%)	
Size			
T1	1 (4.2%)	1 (4.2%)	0.469
T2	6 (27.3%)	12 (50%)	
T3	7 (31.8%)	5 (20.8%)	
T4	8 (36.4%)	6 (25.2%)	
ER			
Positive	9 (40.9%)	12 (50%)	0.536
Negative	13 (59.1%)	12 (50%)	
PR			
Positive	9 (40.9%)	10 (41.7%)	0.958
Negative	13 (59.1%)	14 (58.3%)	
HER 2			
Positive	9 (40.9%)	9 (37.5%)	0.555
Negative	13 (59.1%)	15 (62.5%)	
KI 67			
> 20%	19 (86.4%)	16 (66.7%)	0.118
≤ 20%	3 (13.6%)	8 (33.2%)	
TIL			
Positive	5 (22.7%)	12 (50%)	0.056
Negative	17 (77.3%)	12 (50%)	
Cell Type			
NOS	17 (77.3%)	18 (75.0%)	0.252
Special type	1 (4.2%)	1(4.2%)	
Lobular	3 (13.6%)	4 (16.7%)	
Non-invasive	1 (4.5%)	1 (4.2%)	
Histology Grade			
1	2 (10%)	2 (8.3%)	0.995
2	9 (40%)	10 (41.7%)	
3	11 (50%)	12 (50%)	
LVI			
Positive	12 (54.5%)	4 (16.7%)	0.007*
Negative	10 (45.5%)	20 (83.3%)	
HIF-1α			
2	3 (13,6%)	19 (79,2%)	< 0.001*
3	19 (86,4%)	5 (20,8%)	
HIF1α score (mean ± SB)	7,75 ± 1,61	5,33 ± 1,70	< 0.001*

HER2: Human Epidermal Growth Factor Receptor 2; LVI: Lymphovascular Invasion; HIF-1α: Hypoxia-Inducible Factor 1-alpha
*Significant

Table 2. Sensitivity, specificity, and cut-off points of the HIF-1α score

Variables	AUC	95% CI	Sensitivity (%)	Specificity (%)	Cut-off points	P
HIF-1α	82.7%	70.3-95.1	86.4	79.2	5.4	< 0.001

AUC: Area under curve; CI: confidence interval; HIF-1α: Hypoxia-Inducible Factor 1-alpha
*Significant

Table 3. Risk of high HIF-1α with axillary lymph nodes metastasis

Variables	Lymph nodes		OR	95% CI	P
	Case n = 22	Control n = 24			
HIF-1α					
Score ≥ 5.4 (high risk)	19 (86.4)	5 (20.8)	24.01	5.03–115.25	< 0.001
Score < 5.4 (low risk)	3 (13.6)	19 (79.2)			

CI: confidence interval; HIF-1α: Hypoxia-Inducible Factor 1-alpha; OR: odds-ratio

Table 4. Risk of LVI (+) with axilla lymph nodes metastasis

Variables	Lymph nodes		OR	95% CI	P
	Case n = 22	Control n = 24			
LVI					
Positive (high risk)	12 (54.5%)	4 (16.7%)	6	1.53–23.44	0.007
Negative (low risk)	10 (45.5%)	20 (83.3%)			

CI: confidence interval; LVI: lymphovascular invasion; OR: odds-ratio

Table 5. Multivariate analysis results with high HIF-1α and LVI (+)

Variables	B	S.E	aOR	95% CI	P
LVI	0.690	0.562	4.334	2.369–6.053	0.025*
HIF-1α	3.181	0.799	24.067	5.026–115.247	< 0.001*

LVI: Lymphovascular Invasion; HIF-1α: Hypoxia-Inducible Factor 1-alpha
*Significant with p < 0.05

metastasis in HR-/HER2- patients [22]. Lymph node metastasis differs according to the molecular subtype of breast cancer. Luminal types tend to have a higher incidence of lymph node metastasis than HER2 or TNBC. The ratio of nodal metastasis to tumor size (Np/T), which indicates the effect of nodal metastasis adjusted for tumor size, these findings suggest that breast cancer subtype influences the regional management of axillary lymph nodes metastasis [23].

The case group in this study found that the most size was T4 (36.4%) while in the control group the most size was T2 (50), the results did not differ from Suanjaya et al. [24], about the characteristics of breast cancer in Mataram city, found that the most case group in Mataram city from 2015 to 2020 was T4 (47, 15%), this is different from research in America from 1990 to 2014 on 819,647 women with breast cancer size 10–15 cm (T3) as much as 0.7% and concluded there was no linear relationship between tumor size and metastasis in invasive ca mamae [24,25]. Tumor distance from the skin is an important predictor of axillary lymph nodes metastasis in invasive breast cancer. The closer the tumor, the incidence of axillary node metastasis [26]. Tumor size is associated with lymphatic invasion, which may reflect lymphatic spread [27].

The case group was found to have 9 (40.9%) positive ER and 13 (59.1%) negative ER, while the control group had 12 (50%) positive ER and 12 (50%) negative ER. This is in accordance with research Sidauruk [28] obtained 98 breast cancer patients at Dr. Pirngadi Medan Hospital, with the most age > 40 years, 76 people (79.2%). The positive estrogen receptor status was 45 people (47%), and the negative was 52 people (53%). Research by Firasi et al. [29] in Dr. Kariadi Semarang Hospital also has similar results; the most estrogen receptor hormonal status is estrogen receptor negative, namely 314 people (70.4%). The older a person gets, the more estrogen exposure they experience [30].

About two-thirds of women with breast cancer entering at menopausal age (49–51 years) have negative estrogen receptor expression, while about 80% of breast cancers in postmenopausal women aged > 51 years are estrogen receptor positive [30]. Postmenopausal women have a 2.25 times greater risk of developing breast cancer than premenopausal women. Menopausal status showed significant differences in estrogen receptor

expression based on the results of multivariate analysis with a p value of 0.04 [31]. Results in research Sari et al. [32] also found that patients with post-menopausal status tend to have positive estrogen receptor expression so that the prognosis in patients with postmenopausal status is better than pre-menopausal patients. The high levels of estrogen in post-menopausal women are due to the high uptake of hormones in circulation. In addition, uptake also comes from local synthesis and metabolism of steroids in breast tissue. Several enzymes involved in steroid sex hormone metabolism (aromatase, sulfatase, sulfotransferase, 17-hydroxysteroid dehydrogenase) are expressed and functional in both normal and neoplastic breast tissue [33].

Estrogen receptor is one of the main prognostic and predictive factors examined in breast cancer [34]. Estrogen receptor is one of the main factors examined in breast cancer and can be one of the determinants of hormonal therapy in patients [35]. This receptor is overexpressed in about 70% of breast cancers known as Estrogen Receptor Positive [36]. About 2/3 of women with breast cancer aged < 50 years have estrogen receptor negative, and about 80% of women aged > 50 years have estrogen receptor positive [35].

In this study, negative progesterone expression was the highest. Progesterone receptors were found in the cytoplasm of target cells. Strong progesterone expression was found in 25% of patients with stage III, and had a survival risk of 4.9 times < 5 years [37]. In a study conducted by Willibald et al. [38] before neoadjuvant therapy, strong progesterone levels in 59 people (85.5%) decreased significantly, with a significant p < 0.001 after therapy. In the study of Barbano et al. [39], strong progesterone expression found in 39 breast cancer patients (53%) was significantly associated with high RAD51 mRNA expression [38,39]. Progesterone enters the cell through a diffusion process. There are 2 types of progesterone receptors, namely progesterone receptor A (PRA) and progesterone receptor B (PRB). Both receptors cause transcription of certain genes that have estrogen-specific expression. It is suspected that PRA inhibits the effects of PRB, and the inhibition extends to affect estrogen [40]. The inhibitory effect of PRA on sex steroids is utilized to counteract the endometrial proliferation effect of estrogen with the use of TSH [41].

The case group was found to have positive HER2 9 (40.9%) subjects and negative HER2 13 (59.1%) subjects, while the control group had positive HER2 9 (37.5%) subjects and negative HER2 15 (62.5%) subjects. Based on data from the Cancer Registry of the Indonesian Society of Oncology Surgeons from January 1, 2020, to December 31, 2021, there were 451 cases with positive HER-2 in 91 cases (20.1%). HER-2/neu is a proto-oncogene that encodes a transmembrane tyrosine kinase receptor and is involved in several pathways regulating breast cancer cell proliferation, survival, and invasion. Overexpression or amplification of expression is reported in 10% to 34% of invasive breast cancers. HER2 is an important prognostic factor in both lymph node-positive and lymph node-negative patients [42]. In a study conducted by Serrano-Gomez et al. [43] in Colombia HER 2 positive only (8.6%) of 3764 patients with breast cancer, as well as the study of Abubakar et al. [44] of 3,012 patients in Sarawak, Malaysia, HER2 positivity was only (15%), and in Widiana et al. [45] research stated that based on immunohistochemical examination (IHK), in breast cancer subtypes in Indonesia, the HER2 subtype was around 214 (21.7%). HER2 expression is associated with a significant increase in the metastatic potential of breast cancer cells and can be a strong indicator of regional and distant breast cancer metastasis.

Ki67 protein was > 20% in both groups. High Ki-67 in HER2/neu and metaplastic TNBC subtypes, and all these breast cancer categories are uniformly considered as aggressive breast cancer phenotypes. In addition, the significant association of Ki-67 index with tumor grade is considered as one of the prognostic factors in breast cancer, but Ki-67 has no significant association with other prognostic parameters, including nodal metastasis [46]. Ki67 is a protein found on the surface of cells; this test determines the rate of cell division (how aggressive the cell development is) in the tissue sample examined. The higher the Ki67 result, indicates more aggressive the cancer cell development. In Asri et al. [47], only found 1 breast cancer patient was found with high Ki-67 protein results, so there was a correlation between Ki-67 expression with the degree of differentiation and lymphovascular invasion in TNBC breast cancer. Sitompul et al. [48] research on breast cancer patients at the Haji Adam Malik Medan Hospital found a significant relationship between Ki-67 expression and axillary lymph nodes metastasis where if Ki-67 expression is high then metastasis increases.

The case group was found to have positive tumor-infiltrating lymphocytes (TIL) in 5 (22.7%) subjects and negative TIL in 17 (77.3%) subjects, while the control group had positive TIL in 12 (50%) subjects and negative TIL in 12 (50%). These results are in accordance with the research of Criscitiello et al. [49] with the results of higher TILs positively associated with the number of lymph nodes involved (p = 0.003), tumor size (p < 0.0001), peritumoral vascular invasion (p = 0.003), high Ki-67 (p = 0.0001), luminal B subtype (p < 0.0001), high TILs in ER+/HER2- significantly associated with clinico-pathological features and poor prognosis. Correlation between lymph nodes metastasis and tumor immune microenvironment in cT1 breast cancer, TIL density may be a predictor of sentinel lymph nodes metastases in breast cancer without lymph nodes metastasis on preoperative imaging [50].

The most common cell type in both groups was the Not Otherwise Specified (NOS) type. The results of this

study are in accordance with the majority at Prof IGNG Ngoerah Denpasar Hospital from 2014 to 2018, with the results of 78% of 46 research subjects with NOS type.[50] "Not Otherwise Specified Type" or "NOS" stands for "Not Otherwise Specified" or "not specified." The term NOS is used to describe types of breast cancer that cannot be categorized into a particular type of breast cancer [51].

Archival data from the Department of Anatomic Pathology FKUI/RSCM showed that the most common histologic subtype of invasive breast carcinoma was No Special Type (NST), with 571 cases (87.6%). The second most common subtype was lobular type, with 27 cases (4.1%), followed by the mucinous subtype with 15 cases (2.3%). Mixed carcinomas include NST and invasive lobular carcinoma, NST and mucinous carcinoma [52].

The most histopathologic grade was grade III. This result is in accordance with research by Prawirohardjo et al. [53]. Grade I, there were 2 people (6.7%), Grade II, there were 8 people (26.7%), and the degree of cell differentiation in grade III category was 20 people (66.7%). Grading was associated with 10-year life expectancy, where grade I (85%), grade II (60%), and grade III (45%). Grade I showed the best prognosis, grade II showed a moderate prognosis, while grade III showed the worst prognosis [54]. According to research by Jonjić et al. [55], tumor grading was associated with lymphovascular infiltration, i.e., cases with lymphovascular infiltration were grade III cases. In the study of Firdaus et al. [41], people (62.1%) had histopathological grading in grade II in invasive breast cancer in the surgical department of Dr. M. Djamil Padang Hospital for the period January 1, 2010, to December 31, 2013 [56]. In research conducted by Haholongan et al. [57] in Dr. Soetomo Surabaya Hospital, a high histopathological grading was obtained (34.6%). Based on research by Dedy et al. [58], it was found that most types of cancer were invasive ductal carcinoma. Histologically, the highest number of grade 3 breast cancer cases was found. The tumor size was obtained at T2 in 40 patients (86.3%). From the assessment of histological examination and sentinel biopsy examination, it was found that there was an association between histological grading and the occurrence of sentinel lymph node metastasis (p = 0.001) [58]. Higher histologic grading (grade 3) was statistically significantly associated with axillary lymph nodes metastasis [59].

The case group was found to have positive LVI 12 (54.5%) subjects and negative LVI 10 (45.5%) subjects, while the control group had positive LVI 4 (16.7%) subjects and negative LVI 20 (83.3%), with a value of p = 0.007. LVI (+) has a risk of metastasis to axilla lymph nodes (+) of 6 times (95% CI 1.53–23.44, p = 0.007) and aOR 4.33 (95% CI 2.369–6.053; p = 0.025). The results of this study are in accordance with the study of García-Fernández et al. [60] that lymphovascular invasion was associated with metastasis to lymph nodes (+) and a three-fold higher mortality rate compared to that without invasion. The significance of lymphovascular invasion was noted in univariate and multivariate analysis, suggesting that LVI has a prognostic role in breast cancer survival [61]. Similar results to the study of Song et al. [62], who showed that Lymphovascular Invasion (LVI) also acts as a poor prognostic factor in patients with invasive breast cancer. In a study conducted by He et al. [63] stated that LVI in breast cancer patients was associated with high histological grade (p = 0.003), lymph nodes involvement (p < 0.001), and recurrence of the tumor (p < 0.001).

Cancer cell migration is an early process of carcinogenesis, and all invasive tumors show migration ability. Cell migration is an important step in disease progression and can be considered the initial stage of LVI and tumor metastasis [64].

LVI is one of the prognostic factors that can be used to determine the administration of more aggressive adjuvant systemic chemotherapy in patients with breast cancer, the presence of LVI can be a marker of an increased risk of lymph nodes metastasis as well as distant metastasis and is a significant independent prognostic factor for disease-free survival (p < 0.001) and overall survival (p = 0.006) [62].

Tumor cells can invade lymphatic vessels, allowing them to penetrate the lymphatic system. Growth of lymphatic vessels near solid tumors is often associated with lymph node metastasis. The presence of lymphatic invasion in breast cancer may be a potential indicator of the ability of breast cancer cells to metastasize to the lymph nodes. Lymphatic invasion may represent the selective affinity of breast cancer cells for lymph nodes [65]. On the other hand, tumor cells invading blood vessels are important markers of systemic spread and metastasis. Vascular invasion is considered more meaningful for predicting disease recurrence or prognosis than lymphatic invasion. In a study conducted by Fujii et al. [27], revealed that lymphatic invasion and vascular invasion were statistically significant, but multivariate analysis showed that only vascular invasion (p = 0.004) was an independent negative prognostic factor. In 91 patients without lymphatic invasion and vascular invasion (ly-/v-), 5 (5.5%) of them experienced disease recurrence, and of 73 patients with ly+/v-, 5 (6.8%) experienced disease recurrence. In contrast, in 95 patients with ly+/v+, 19 (20.0%) experienced recurrence, and of the 3 patients with ly-/v+, 1 experienced recurrence. Fujii et al. [27] concluded that lymphatic invasion without vascular invasion does not affect the risk of disease recurrence or prognosis.

Despite the differences in opinion, it is broadly stated that LVI is a significant predictor of axillary metastasis and a poorer prognosis. The presence of LVI is significantly associated with shorter disease-free intervals

P-ISSN: 1978-3744 E-ISSN: 2355-6811

and recurrence rates. In a study conducted by Gurleyik et al. [66] found that LVI had an association with axillary involvement, where the level of LVI (+) gradually increased with the number of lymph nodes involved. Axillary status indicates the metastatic ability (systemic spread) of the primary breast malignancy. Our LVI results also support the predictive power of LVI regarding metastatic potential. In a study conducted by Schoppmann et al. [67], it was also stated that the determination of lymphatic microvessel density and LVI predicted high metastatic potential in breast cancer, and LVI was significantly associated with a higher risk of developing lymph node metastases [67,68].

The case group was found to have HIF1α with a mean ± SB score of 7.75 ± 1.61 with category 2 found in 3 (13.6%) subjects and category 3 as many as 19 (86.4%) subjects while the control group had a mean ± SB score of 5.33 ± 1.70 with category 2 found in 19 (79.2%) subjects and category 3 as many as 5 (20.8%) with a p value < 0.001. The ROC curve results obtained a sensitivity value of 86.4% and specificity of 79.2% with a cut-off value of 5.4. A score ≥ 5.4 has a risk of metastasis to axilla lymph nodes (+) of 24.01 times (95% CI 5.03–115.25; p < 0.001) and aOR 24.06 (95% CI 5.026–115.247; p < 0.001). The results of this study are in accordance with Liu et al. [69], which states that HIF-1α regulates lymph node metastasis by several mechanisms, such as mediating epithelial-mesenchymal transition (EMT), invasion, intravasation, and extravasation. In a study using mouse trials, it was found that inhibition of HIF-1α activity in triple-negative breast cancer cells had a dramatic effect on primary tumor growth as well as metastasis to lymph nodes and lungs. HIF-1α functions as a mediator that regulates the transcription of adaptive responses to hypoxia. In hypoxic conditions, cell proliferation does not occur, but it will induce HIF to increase metabolic processes, angiogenesis, and cell division [70].

HIF-1α is a transcription factor that facilitates cancer cell adaptation to hypoxic conditions and may be a prognostic factor of breast cancer recurrence [71]. A recent Danish population-based case-control study evaluated the association of HIF-1α expression with breast cancer recurrence and its relationship with the timing of breast cancer recurrence. The study found that HIF-1α expression was not associated with overall breast cancer recurrence but may be associated with early recurrence in women diagnosed with ER breast cancer [72]. In TNBC, FBXL16 expression is downregulated by the p38/miR-135b-3p axis, and loss of FBXL16 expression restores HIF1α-mediated metastatic features in breast cancer [59]. Badowska, et al. (2018) study included 162 breast cancer patients, finding 111 (68.5%) subjects with triple-negative breast cancer, G2 and G3 (52.2%; 45.1%), pT1 and pT2 (34.2%; 62.1%), and pN1 and pN2 (45%; 41.4%). TNBC displayed HIF-1α expression more frequently (43.2%) than non-TNBC (35.2%). A statistically significant association was found between HIF-1α expression in patients diagnosed with triple-negative breast cancer with lymph node metastasis [73].

Cai et al. [74] in 2016 analyzed plasma samples of 297 female patients, with 267 breast cancer patients and 30 benign breast tumor patients to investigate the role of HIF-1α, as well as PGC-1α, in tumorigenesis, growth, and metastasis of breast cancer [74]. High levels of HIF-1α and PGC-1α were associated with more aggressive types of breast cancer. This suggests that HIF-1α and PGC-1α may stimulate tumor progression and metastasis, and have the power to predict prognosis in breast cancer patients.

This study has several strengths. It offers a comprehensive molecular subtype analysis, providing valuable insights into the relationship between breast cancer subtypes and axillary lymph node involvement, which enhances our understanding of tumor behavior. Additionally, the use of real-world clinical data from a tertiary hospital offers practical insights into treatment responses and prognostic factors specific to the studied population. The study also incorporates multiple prognostic markers—including ER, PR, HER2, Ki-67, and LVI—allowing for a detailed exploration of their correlations with nodal metastasis, contributing to better clinical decision-making. Moreover, the findings reflect context-specific relevance by focusing on trends within a Southeast Asian population, addressing gaps in global literature by emphasizing region-specific patterns.

However, there are also limitations to consider. The single-center nature of the study may limit the generalizability of the findings to other healthcare settings with different populations and protocols. As a retrospective study, it is subject to selection bias and the possibility of missing data, which may affect the reliability of the results. The limited sample size also reduces the statistical power, particularly for subgroup analyses of molecular subtypes and clinicopathological characteristics. Furthermore, the study does not include survival analysis, restricting its utility in predicting long-term outcomes. Lastly, the heterogeneity of treatment modalities, such as variations in chemotherapy or hormonal therapy, was not controlled for, which could influence the observed associations between tumor markers and nodal involvement.

CONCLUSIONS

Breast cancer patients with high HIF-1α expression, defined as a score of ≥ 5.4, have a significantly increased risk of axillary lymph node metastasis, with an odds

ratio of 24.01 times higher compared to those exhibiting low HIF-1α expression. Additionally, breast cancer patients with LVI positive status demonstrate a sixfold greater risk of axillary lymph node metastasis compared to their counterparts with negative LVI status.

DECLARATIONS

Competing interest
The author(s) declared that no conflicts of interest.

Ethics approval and consent to participate
Research ethics permit from the Ethics Committee of the Faculty of Medicine, Udayana University, with Number 3162/UN14.2.2.VII.14/LT/2022.

Funding
None.

Acknowledgment
None.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clinicians. 2018;68:394–424.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA A Cancer J Clinicians. 2021;71:209–49.
3. Lobbezoo DJA, van Kampen RJW, Voogd AC, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer. 2015;112:1445–51.
4. Chan IS, Knútsdóttir H, Ramakrishnan G, et al. Cancer cells educate natural killer cells to a metastasis-promoting cell state. J Cell Biol. 2020;219:e202001134.
5. Blanco MA, Kang Y. Signaling pathways in breast cancer metastasis - novel insights from functional genomics. Breast Cancer Res. 2011;13:206.
6. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022;12:31–46.
7. Gao Y, Bado I, Wang H, et al. Metastasis Organotropism: Redefining the Congenial Soil. Dev Cell. 2019;49:375–91.
8. Madu CO, Wang S, Madu CO, Lu Y. Angiogenesis in Breast Cancer Progression, Diagnosis, and Treatment. J Cancer. 2020;11:4474–94.
9. Pezzuto A, Carico E. Role of HIF-1 in Cancer Progression: Novel Insights. A Review. Curr Mol Med. 2018;18:343–51.
10. Zhang Y, Zhang H, Wang M, et al. Hypoxia in Breast Cancer—Scientific Translation to Therapeutic and Diagnostic Clinical Applications. Front Oncol. 2021;11:652266.
11. Joseph C, Alsaleem M, Orah N, et al. Elevated MMP9 expression in breast cancer is a predictor of shorter patient survival. Breast Cancer Res Treat. 2020;182:267–82.
12. Verdial FC, Mamtani A, Pawloski KR, et al. The Effect of Age on Outcomes After Neoadjuvant Chemotherapy for Breast Cancer. Ann Surg Oncol. 2022;29:3810–9.
13. Aryana IGPS, Adiputra PAT, Permatasari Y, et al. Breast Cancer in Older Women at Sanglah Central General Hospital. E-journal Medika Udayana. 2014;3:1–9.
14. Narisuari IDAPM, Manuaba IBTW. P Prevalence and characteristics of breast cancer patients in the oncology surgery polyclinic of Sanglah General Hospital, Bali, Indonesia in 2016. Medical Science Digest. 2020;11:183–9.
15. Aryawan ITK. Characteristics Based on Immunohistochemical Examination and Sociodemography in Breast Cancer Patients at Sanglah Central General Hospital Denpasar in 2009-2013. 2018;7:1–6.
16. World Health Organization. Breast Cancer. 2020; Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer
17. Ribnikar D, Ribeiro JM, Pinto D, et al. Breast cancer under age 40: a different approach. Curr Treat Options Oncol. 2015;16:16.
18. Kashyap D, Bal A, Irinike S, et al. Heterogeneity of the Tumor Microenvironment Across Molecular Subtypes of Breast Cancer. Appl Immunohistochem Mol Morphol. 2023;31:533–43.
19. Yin L, Duan JJ, Bian X-W, Yu S-C. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res. 2020;22:61.
20. Yang R, Li Y, Wang H, et al. Therapeutic progress and challenges for triple negative breast cancer: targeted therapy and immunotherapy. Mol Biomed. 2022;3:8.
21. YY S, PU P. Molecular Subtypes of Invasive Breast Cancer Patients: A Systematic Review of Literature Association Of Lymphovascular Infiltration With Molecular Subtypes Of Invasive Breast Cancer: A Systematic Review. 2021;9:15–22.
22. Armer JM, Henggeler MH, Brooks CW, et al. The Health Deviation of Post-Breast Cancer Lymphedema: Symptom Assessment and Impact on Self-Care Agency. Self Care Depend Care Nurs. 2008;16:14–21.
23. Min SK, Lee SK, Woo J, et al. Relation Between Tumor Size and Lymph Node Metastasis According to Subtypes of Breast Cancer. J Breast Cancer. 2021;24:75.

24. Suanjaya MA, Sherliyanah S, Utami S. Prevalence and Characteristics of Breast Cancer Patients in Mataram City for the 2015-2020 Period. Jurnal Aisyah: Jurnal Ilmu Kesehatan. 2021;6.
25. Sopik V, Narod SA. The relationship between tumour size, nodal status and distant metastases: on the origins of breast cancer. Breast Cancer Res Treat. 2018;170:647–56.
26. Ojha SS, Jain RA, Nilkanthe RG, et al. Distance of Tumor to Skin as a Predictive Marker for Axillary Lymph Node Metastasis in Cases of Breast Carcinoma - A Retrospective Study. Indian Journal of Medical and Paediatric Oncology. 2018;39:321–5.
27. Fujii T, Yajima R, Hirakata T, et al. Impact of the prognostic value of vascular invasion, but not lymphatic invasion, of the primary tumor in patients with breast cancer. Anticancer Res. 2014;34:1255–9.
28. Sidauruk JTS. H Relationship between Age and Estrogen Receptor in Breast Cancer Patients at Dr. Pirngadi Medan Hospital in 2018. Nommensen Journal of Medicine. 2020;6(1):1-4.
29. Firasi AA, Yudhanto E. Relationship of Age To The Degree of Difference of Breast Cancer In Women. 2016;5.
30. Payne SJL, Bowen RL, Jones JL, Wells CA. Predictive markers in breast cancer--the present. Histopathology. 2008;52:82–90.
31. Thornton MJ. Estrogens and aging skin. Dermatoendocrinol. 2013;5:264–70.
32. Sari SE, Harahap WA, Saputra D. Effect of Risk Factors on Estrogen Receptor Expression in Breast Cancer Patients in Padang City. Andalas Health Journal. 2018;7:461.
33. Falk RT, Gentzschein E, Stanczyk FZ, et al. Measurement of sex steroid hormones in breast adipocytes: methods and implications. Cancer Epidemiol Biomarkers Prev. 2008 Aug;17(8):1891-5.
34. Fujimoto Y, Watanabe T, Hida AI, et al. Prognostic significance of tumor-infiltrating lymphocytes may differ depending on Ki67 expression levels in estrogen receptor-positive/HER2-negative operated breast cancers. Breast Cancer. 2019;26:738–47.
35. Putri NMA, Kurniati YP. Relationship Between Age and Body Mass Index (BMI) with Estrogen Receptor (ER) Molecular Phenotype in Invasive Breast Carsinoma of No Special Type (NST) Patients at PKU Muhammadiyah Surakarta Hospital[Thesis]. Universitas Muhammadiyah Surakarta. 2018;1:1–78.
36. Honda C, Kurozumi S, Katayama A, et al. Prognostic value of tumor-infiltrating lymphocytes in estrogen receptor-positive and human epidermal growth factor receptor 2-negative breast cancer. Mol Clin Oncol. 2021;15:252.
37. Finn RS, Press MF, Dering J, et al. Estrogen Receptor, Progesterone Receptor, Human Epidermal Growth Factor Receptor 2 (HER2), and Epidermal Growth Factor Receptor Expression and Benefit From Lapatinib in a Randomized Trial of Paclitaxel With Lapatinib or Placebo As First-Line Treatment in HER2-Negative or Unknown Metastatic Breast Cancer. JCO. 2009;27:3908–15.
38. Willibald M, Wurster I, Meisner C, et al. High Level of Progesteron Receptor Membrane Component 1 (PGRMC 1) in Tissue of Breast Cancer Patients is Associated with Worse Response to Anthracycline-Based Neoadjuvant Therapy. Horm Metab Res. 2017;49:595–603.
39. Barbano R, Copetti M, Perrone G, et al. High RAD51 mRNA expression characterize estrogen receptor-positive/progesteron receptor-negative breast cancer and is associated with patient's outcome. Int J Cancer. 2011;129:536–45.
40. Viale G, Regan MM, Maiorano E, et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98. J Clin Oncol. 2007;25:3846–52.
41. Calabrò A, Beissbarth T, Kuner R, et al. Effects of infiltrating lymphocytes and estrogen receptor on gene expression and prognosis in breast cancer. Breast Cancer Res Treat. 2009;116:69–77.
42. dos Santos GT, Camillo ND, Berto MD, et al. Impact of Her-2 Overexpression on Survival of Patients with Metastatic Breast Cancer. Asian Pac J Cancer Prev. 2017;18:2673–8.
43. Serrano-Gomez SJ, Sanabria-Salas MC, Hernández-Suarez G, et al. High prevalence of luminal B breast cancer intrinsic subtype in Colombian women. Carcinogenesis. 2016;37:669–76.
44. Abubakar M, Sung H, Bcr D, et al. Breast cancer risk factors, survival and recurrence, and tumor molecular subtype: analysis of 3012 women from an indigenous Asian population. Breast Cancer Res. 2018;20:114.
45. Widiana IK, Irawan H. Clinical and Subtypes of Breast Cancer in Indonesia. Asian Pac J Cancer Care. 2020;5:281–5.
46. Cheang MCU, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101:736–50.
47. Asri A, Mayorita P, Khambri D. Relationship of Ki-67 Expression with Histopathologic Characteristics in Triple Negative Breast Cancer. Andalas Medical Magazine. 2015;38:165.
48. Sitompul O. The Relationship of Ki-67 Expression with Axillary Lymph Node Metastasis in Breast Cancer Patients at Haji Adam Malik Hospital Medan. University of North Sumatra Institutional Repository (RI-USU) [Internet]. 2017; Available from: https://repositori.usu.ac.id/handle/123456789/51264

49. Criscitiello C, Vingiani A, Maisonneuve P, et al. Tumor-infiltrating lymphocytes (TILs) in ER+/HER2− breast cancer. Breast Cancer Res Treat. 2020;183:347–54.
50. Takada M, Toi M. Neoadjuvant treatment for HER2-positive breast cancer. Chin Clin Oncol. 2020;9:32.
51. Rojas K, Stuckey A. Breast Cancer Epidemiology and Risk Factors. Clin Obstet Gynecol. 2016 Dec;59(4): 651–672.
52. Bethania KA, Rustamadji P. Association between Molecular Subtype of Invasive Breast Carcinoma with grade, lymphovascular invasion and lymph node metastasis in the Department of Anatomic Pathology FKUI/RSCM 2019. MPI. 2022;31:392–9.
53. Prawirohardjo AN, Soewoto W, Alfianto U. H Relationship between body mass index and grading in breast cancer. Biomedika. 2018;10.
54. Das S, Sen S, Mukherjee A, et al. Risk factors of breast cancer among women in eastern India: a tertiary hospital based case control study. Asian Pac J Cancer Prev. 2012;13:4979–81.
55. Jonjic N, Mustac E, Dekanic A, et al. Predicting sentinel lymph node metastases in infiltrating breast carcinoma with vascular invasion. Int J Surg Pathol. 2006;14:306–11.
56. Firdaus VRP, Asri A, Khambri D, Harahap WA. H Relationship between Histopathology Grading and Lymphovascular Infiltration with Molecular Subtypes in Invasive Breast Cancer in the Surgery Department of RSUP. Dr. M. Djamil Padang. Andalas Health Journal. 2016;5.
57. Haholongan DD, Ali I, Tanggo EH. Relationship of Obesity Recurrence Events in Triple Negative Breast Cancer Patients in Dr. Soetomo General Hospital Surabaya. IJPHRD. 2020;
58. Hermansyah D, Firsty NN. The Role of Breast Imaging in Pre- and Post-Definitive Treatment of Breast Cancer. Exon Publications. 2022;83–99.
59. Kim YJ, Zhao Y, Myung JK, et al. Suppression of breast cancer progression by FBXL16 via oxygen-independent regulation of HIF1α stability. Cell Rep. 2021;37:109996.
60. García-Fernández A, Barco I, Fraile M, et al. Factors predictive of mortality in a cohort of women surgically treated for breast cancer from 1997 to 2014. Int J Gynaecol Obstet. 2016;134:212–6.
61. Aleskandarany MA, Sonbul SN, Mukherjee A, Rakha EA. Molecular Mechanisms Underlying Lympho-vascular Invasion in Invasive Breast Cancer. Pathobiology. 2015;82:113–23.
62. Song YJ, Shin SH, Cho JS, et al. The role of lymphovascular invasion as a prognostic factor in patients with lymph node-positive operable invasive breast cancer. J Breast Cancer. 2011;14:198–203.
63. He KW, Sun JJ, Liu ZB, et al. Prognostic significance of lymphatic vessel invasion diagnosed by D2-40 in Chinese invasive breast cancers. Medicine. 2017;96:e8490.
64. Feig B, Ching C, Kwon D, et al. Invasive Breast Cancer. The MD Anderson Surgical Oncology Handbook. 6th ed. Texas: Lippicott William and Wilkin; 2018. p. 36.
65. Shea EKH, Koh VCY, Tan PH. Invasive breast cancer: Current perspectives and emerging views. Pathol Int. 2020;70:242–52.
66. Gurleyik G, Gurleyik E, Aker F, et al. Lymphovascular invasion, as a prognostic marker in patients with invasive breast cancer. Acta Chir Belg. 2007;107: 284–7.
67. Schoppmann SF, Bayer G, Aumayr K, et al. Prognostic Value of Lymphangiogenesis and Lymphovascular Invasion in Invasive Breast Cancer. Ann Surg. 2004;240:306–12.
68. Zhang H, Wong CCL, Wei H, et al. HIF-1-dependent expression of angiopoietin-like 4 and L1CAM mediates vascular metastasis of hypoxic breast cancer cells to the lungs. Oncogene. 2012;31:1757–70.
69. Liu Z, Semenza GL, Zhang H. Hypoxia-inducible factor 1 and breast cancer metastasis. J Zhejiang Univ Sci B. 2015;16:32–43.
70. Foxler DE, Bridge KS, James V, et al. The LIMD1 protein bridges an association between the prolyl hydroxylases and VHL to repress HIF-1 activity. Nat Cell Biol. 2012;14:201–8.
71. Ren Z, Dharmaratne M, Liang H, et al. Redox signalling regulates breast cancer metastasis via phenotypic and metabolic reprogramming due to p63 activation by HIF1α. Br J Cancer. 2024 Apr;130(6):908–924.
72. Collin LJ, Maliniak ML, Cronin-Fenton DP, et al. Hypoxia-inducible factor-1α expression and breast cancer recurrence in a Danish population-based case control study. Breast Cancer Res. 2021;23:103.
73. Maria Badowska-Kozakiewicz A, Piotr Budzik M. Triple-Negative Breast Cancer: Expression of Hypoxia-Inducible Factor 1α in Triple-Negative Breast Cancer with Metastasis to Lymph Nodes. In: Bulut N, editor. Breast Cancer and Surgery [Internet]. IntechOpen; 2018 [cited 2024 Sep 4]. Available from: https://www.intechopen.com/books/breast-cancer-and-surgery/triple-negative-breast-cancer-expression-of-hypoxia-inducible-factor-1-in-triple-negative-breast-can
74. Cai FF, Xu C, Pan X, Cai L, et al. Prognostic value of plasma levels of HIF-1a and PGC-1a in breast cancer. Oncotarget. 2016;7:77793–x806.