DOI:10.31557/APJCB.2025.10.4.921

RESEARCH ARTICLE

YAP1 Immunoexpression as a Biomarker of Histological Grade, Lymph Node Metastasis, and Lymphovascular Invasion in Invasive Breast Carcinoma

Yulianti Redjeb[1], Berti Julian Nelwan[1,2], Muhammad Husni Cangara[1,2], Upik Andriani Miskad[1,2], Djumadi Achmad[1,2], Amalia Yamin[1,3], Suryani Tawali[4]

[1]Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. [2]Anatomical Pathology Laboratory, Hasanuddin University Hospital, Makassar, Indonesia. [3]Anatomical Pathology Laboratory, Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia. [4]Department of Public Health, Hasanuddin University, Makassar, Indonesia.

Abstract

Objective: This research seeks to assess the relationship between YAP1 expression and histological grading, lymphovascular invasion, and lymph node metastasis in patients with invasive breast cancer in Makassar, a study that has not been previously performed. **Methods:** A cross-sectional study was carried out on 100 mastectomy samples identified as invasive breast carcinoma at Dr. Wahidin Sudirohosodo Hospital, Makassar, Indonesia. YAP1 expression was assessed through immunohistochemistry and scored according to the immunoreactive score (IRS) method. A statistical evaluation was conducted using Fisher's exact test. **Result:** The average age of patients was 50.22 ± 10.20 years. YAP1 expression was positive in every instance, with 72% showing strong expression (+3), 25% exhibiting moderate expression (+2), and 3% demonstrating weak expression (+1). A significant correlation existed between YAP1 expression and histological grade (p=0.001), showing increased expression in grade 3 tumors. Nonetheless, no significant correlation was discovered between YAP1 expression and lymph node metastasis (p=0.912) or lymphovascular invasion (p=0.276). **Conclusion:** YAP1 expression shows a strong correlation with histological grade in invasive breast cancer, indicating its potential as a biomarker for tumor aggressiveness. Nonetheless, YAP1 expression is not directly linked to lymph node metastasis or lymphovascular invasion.

Keywords: YAP1- Histological Grading- Lymph Node Spread- Lymphatic Vascular Invasion

Asian Pac J Cancer Biol, **10 (4)**, 921-925

Submission Date: 09/02/2025 Acceptance Date: 10/10/2025

Introduction

Invasive breast carcinoma (IBC) denotes a diverse and extensive collection of malignant tumors arising from the epithelium of the mammary gland. In comparison, invasive breast carcinoma (IBC) of no special type (NST) denotes a category of IBC that cannot be morphologically categorized into a distinct histological type [1].

Metastasis, or the dissemination of tumor cells, can happen through the lymphatic system (lymphogenous) or through the bloodstream (hematogenous). Carcinomas typically spread via the lymphatic system (lymphogenous), with histological analysis being the gold-standard method for identifying metastasis to nearby lymph nodes [2].

Yes-associated protein 1 (YAP1) is a protein that is encoded by chromosome 11q22. YAP1 is pivotal in the Hippo pathway and acts as a transcription co-activator, essential for controlling cell proliferation, apoptosis, and differentiation. Numerous studies have illustrated the involvement of YAP1 in tumorigenesis and the advancement of breast cancer, based on this role. YAP1 levels rise significantly in luminal tumors as a result of p53 loss. The activation of YAP1 as a transcriptional co-activator is essential for promoting proliferation and advancing the tumorigenesis pathway towards invasive lobular carcinoma (ILC). This indicates that YAP1 is

Corresponding Author:
Dr. Berti Julian Nelwan, MD, M.Kes, Sp.PA, Subsp.O.G.P (K), Sp.FM, DFM.
Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.
Email: nelwanb@med.unhas.ac.id

involved in guiding the epithelial carcinoma pathway, its progression, and metastasis [3].

Lymph node metastasis is the key prognostic indicator in breast cancer and relates to recurrence and death rates. Reports indicate that the transcriptional co-activator, YES-associated protein 1 (YAP1), is essential for lymph node metastasis. Elevated YAP1 activity boosts fatty acid oxidation, ultimately resulting in lymph node metastasis. Activation of YAP1 plays a role in the advancement of cancer, such as breast cancer [4, 5]. Information regarding YAP1 expression in breast cancer within Southeast Asia, especially in Makassar, Indonesia, remains scarce; thus, this research significantly enhances the local literature. This research seeks to assess the relationship between YAP1 expression and histological grading, lymphovascular invasion, and lymph node metastasis in patients with invasive breast cancer in Makassar, Indonesia, a subject that has not been explored before.

Materials and Methods

This cross-sectional research took place at the Anatomical Pathology Laboratory of Dr. Wahidin Sudirohosodo Hospital in Makassar, Indonesia, from August 2024 to May 2025. The institutional ethics committee approved the study protocol. The study population comprised paraffin blocks from mastectomy resection specimens submitted to the Anatomical Pathology Laboratory, all diagnosed as invasive breast carcinoma grades 1, 2, and 3, with or without metastasis to regional lymph nodes, utilizing Hematoxylin-Eosin staining. The method of consecutive sampling was employed to choose samples. All instances that satisfied the inclusion criteria were incorporated based on the sequence of tissue arrival at the laboratory from July 2022 to May 2025 until the necessary sample size was achieved. Inclusion criteria: 1) Breast tumor tissue from mastectomy obtained at the Anatomical Pathology Laboratory, accompanied by regional lymph nodes. 2) Identified by pathologists as invasive breast carcinoma grades 1, 2, and 3, with or without metastasis to regional lymph nodes through HE staining. 3) Paraffin blocks appropriate for immunohistochemical analysis. Specimens of paraffin blocks that were depleted or harmed during reprocessing for YAP1 immunohistochemical analysis will be excluded.

Immunohistochemical Staining

The expression of YAP1 was assessed by employing the standard avidin-biotin peroxidase complex (ABC) technique. Tissue slices (4 μm thick) were deparaffinized and underwent antigen retrieval. YAP1 polyclonal antibody was applied at a dilution of 1:50. Findings were assessed through light microscopy by two pathologists, along with the researcher.

YAP1 Expression Scoring

YAP1 intensity is assessed according to a scoring system where 0 = No staining, 1 = Weakly staining, 2 = Moderately staining, and 3 = Strongly staining. Yap1 The proportion of the area that is stained is assessed based on a scoring system: 0 = no tumor cells stained (0%), 1 = 1-10% of tumor cells stained, 2 = 11-25% of tumor cells stained, 3 = 26-50% of tumor cells stained, 4 = 51-100% of tumor cells stained. The IR score results from multiplying intensity by proportion and is classified into various categories: Negative (score 0), +1 (score 1-3), +2 (score 4-6), +3 (score >6).

Histological Grading

Histological grading utilized the Elston and Ellis modification of the Scarff-Bloom-Richardson method, assessing tubule formation, nuclear pleomorphism, and mitotic index.

Statistical Analysis

Data were assessed utilizing SPSS version 26. A descriptive analysis was conducted on patient characteristics. Fisher's exact test was employed to assess the relationship between YAP1 expression and categorical variables. A p-value of less than 0.05 was deemed statistically significant.

Results

Sample Characteristics

This study included a total of 100 specimens from mastectomies. In this research, we evaluated YAP1 expression with low, moderate, and high intensity at 400x magnification, as shown in Figure 1. The average age of patients was 50.22 ± 10.20 years, with 51% of the patients being aged 50 years or older. Table 1 presents a summary of patient characteristics.

YAP1 Expression and Histological Grade

A significant correlation existed between YAP1 expression and histological grade (p=0.001). Elevated

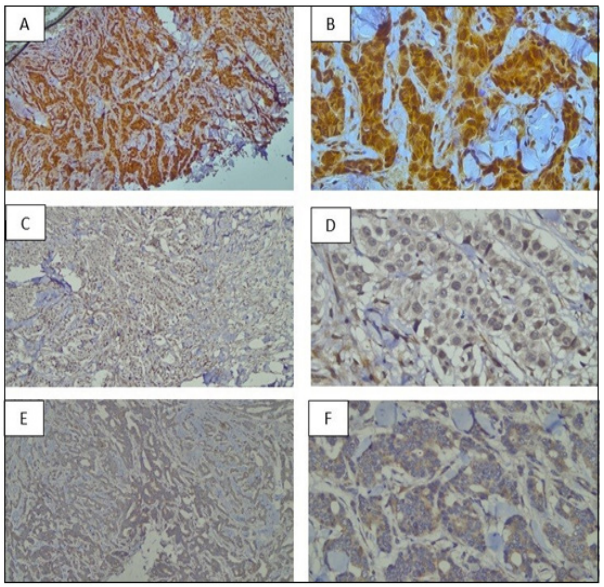

Figure 1. YAP1 Expression in Invasive Breast Cancer. A.Strongly stained (Obj 100x); B. Strongly stained (Obj 40x); C. Moderately stained (Obj 100x); D. Moderately stained (Obj 40x); E. Weakly stained (Obj 10x); F. Weakly stained (Obj 400x). Source: Primary Data, 2024.

Table 1. Sample Characteristics (N=100)

Variable	N (%)
Age (years)	
<50	49 (49.0)
≥50	51 (51.0)
Mean ± SD: 50.22±10.20	
YAP1 Expression	
Negative	0 (0.0)
Positive 1 (+1)	3 (3.0)
Positive 2 (+2)	25 (25.0)
Positive 3 (+3)	72 (72.0)
Histological grade	
Grade 1	13 (13.0)
Grade 2	52 (52.0)
Grade 3	35 (35.0)
Lymph Node Metastasis	
Metastasis	39 (39.0)
Non-metastasis	61 (61.0)
LVI	
Positive	22 (22.0)
Negative	78 (78.0)

N=number of samples; SD=standard deviation; YAP1=YES-associated protein 1; LVI=lymphovascular invasion

YAP1 expression was mainly observed in grade 3 tumors, with 94.3% exhibiting strong YAP1 expression (+3), in contrast to 75% in grade 2 and none in grade 1 tumors Table 2.

YAP1 Expression and Lymph Node Metastasis

No significant correlation was found between YAP1 expression and lymph node metastasis (p-value of 0.912). The expression pattern of YAP1 was comparable in cases both with and without lymph node metastasis Table 3.

YAP1 Expression and Lymphovascular Invasion

No significant correlation was found between YAP1 expression and lymphovascular invasion (p=0.276). YAP1 expression was distributed similarly in cases with lymphovascular invasion and those without, as shown in Table 4.

Discussion

Our findings demonstrate a strong association between YAP1 expression and histological grade in invasive breast cancer, whereas no significant relationships were identified with lymph node metastasis or lymphovascular invasion. This research identified a significant correlation between YAP1 expression and histological grade in invasive breast cancer, yielding a p-value of (0.001). Elevated YAP1 expression, particularly with a positive immunoreactive score of 3 (+3), was predominantly observed in samples exhibiting histological grade 3. This result aligns with an earlier study by Rakha et al. (2012), which indicated that YAP1 expression was markedly elevated in breast cancer tissues exhibiting greater malignancy. Histological grade indicates how differentiated cancer cells are; a higher grade corresponds to a poorer prognosis [1].

In a similar vein, research conducted by Shen, J. et al. (2022) indicated that YAP1 facilitates invadopodia and cell invasion, suggesting that YAP1 plays a role in tumor aggressiveness and offering a direct biological explanation for its association with increased histological grade [6]. Park, I. et al. (2023) conducted a clinical study on YAP1 expression in hormone receptor-positive and HER2-negative breast cancer, examining YAP1's molecular and prognostic implications [7]. Liu D. et al. (2024) demonstrated that metabolic components (DLAT) may trigger the YAP1 signaling pathway in triple-negative breast cancer (TNBC). YAP1 shows high expression in aggressive grades, influenced by both histological factors and upstream metabolic regulation that promotes tumor progression [8]. Bai X. et al. (2024) showed the epitranscriptomic control of YAP1 mediated by METTL14. When METTL14 levels are reduced, YAP1 expression rises, enhancing the stemness and aggressiveness of TNBC. Pertinent to the conversation is that RNA modification mechanisms can affect YAP1 expression, leading to variations among subtypes [9]. Jung O. et al. (2024) outlined a new molecular mechanism through which nuclear phosphoinositides promote the activation of the YAP/TAZ-TEAD complex. Contextualization implies that YAP1 activation might take place via non-classical signaling pathways [10].

This research did not reveal a significant link between YAP1 expression and lymph node metastasis, with a p-value of (0.912). Unlike the research conducted by Cha, Y.J. (2021), which indicated that YAP1 nuclear expression was assessed in numerous breast cancer samples and was significantly linked to the development of distant

Table 2. Correlation Between YAP1 Expression and Histological grade in Invasive Breast Carcinoma (N=100)

YAP1 Expression	Histological grade			Total	p-value
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	(%)	
Positive 1	3 (23.1)	0 (0.0)	0 (0.0)	3 (3.0)	
Positive 2	10 (76.9)	13 (25.0)	2 (5.7)	25 (25.0)	0.001*
Positive 3	0 (0.0)	39 (75.0)	33 (94.3)	72 (72.0)	
Total	13 (100)	52 (100)	35 (100)	100 (100)	

*Fisher exact test, significant if p<0.05; YAP1=YES-associated protein 1

Table 3. Correlation Between YAP1 Expression and Lymph Node Metastasis in Invasive Breast Carcinoma (N=100)

YAP1 Expression	Metastasis		Total	p-value
	Positive	Negative		
	(%)	(%)	(%)	
Positive 1	1 (2.6)	2 (3.3)	3 (3.0)	
Positive 2	9 (23.1)	16 (26.2)	25 (25.0)	0.912*
Positive 3	29 (74.4)	43 (70.5)	72 (72.0)	
Total	39 (100)	61 (100)	100 (100)	

*Fisher exact test, significant if p<0.05; YAP1=YES-associated protein 1; LVI=lymphovascular invasion

Table 4. Correlation Between YAP1 Expression and Lymphovascular Invasion in Invasive Breast Carcinoma (N=100)

YAP1 Expression	LVI		Total	p-value
	Positive	Negative		
	(%)	(%)	(%)	
Positive 1	0 (0.0)	3 (3.8)	3 (3.0)	
Positive 2	8 (36.4)	17 (21.8)	25 (25.0)	0.276*
Positive 3	14 (63.6)	58 (74.4)	72 (72.0)	
Total	22 (100)	78 (100)	100 (100)	

*Fisher exact test, significant if p<0.05; YAP1=YES-associated protein 1; LVI=lymphovascular invasion

metastases [11]. The research conducted by Li, X. et al. (2022) identified contextual YAP in the ER+ subtype, indicating that YAP may act as a tumor suppressor; however, YAP's role varies across subtypes, explaining the differing clinical outcomes observed in various studies [12]. Similarly, the research conducted by Luo, J. et al. (2023) showed that YAP1 was only significant in grading, but not in metastasis or lymphovascular invasion, based on global data, possibly due to subtype heterogeneity [13], while the study by Sadri F. et al. (2023) examined the function of the Hippo-YAP/TAZ pathway in breast cancer, emphasizing its impact on EMT, metastasis, and stem cell-like characteristics [14].

This research indicated that lymph node metastasis also did not show a significant correlation between YAP1 expression and lymphovascular invasion, yielding a p-value of (0.276). In Lee, S.J.'s (2023) research, lymphovascular invasion is identified as an independent adverse prognostic factor for patients with early-stage breast cancer, irrespective of lymph node involvement and molecular subtype [15]. This discrepancy between YAP1 expression and LVI aligns with various other research findings. Asaoka, M. (2021). Breast cancer with LVI exhibits high proliferation and shows no association with gene expression markers related to lymphangiogenesis or immune response [16]. Rakha, E.A. (2012) states that while LVI serves as a robust predictor of outcomes in invasive breast cancer patients, it ought to be incorporated into the breast cancer staging system [1].

Unlike the research by Khalil, A., A., et al. (2024), YAP is engaged in the collective invasion of cells and initiates the mechanotransduction process that promotes invasion [17]. Similarly, the research conducted by Athavale D. et al. (2024) regarding YAP1's relationship with cancer-associated fibroblasts (CAF) and the tumor microenvironment indicates that YAP1 is involved not just in tumor cells but also in its interactions with the stroma, influencing the invasion and aggressiveness of breast cancer [18].

The findings indicated that YAP1 expression was notably linked to histological grade, but not to lymph node metastasis or lymphovascular invasion. The novelty of this research lies in being the first report from Makassar, Indonesia, exploring YAP1 expression in invasive breast carcinoma, thereby enriching regional data on breast cancer biomarkers.

In conclusion, this research shows a strong relationship between YAP1 expression and histological grade in invasive breast cancer, implying YAP1's possible function as a marker for tumor aggressiveness. Nonetheless, YAP1 expression does not seem to be directly linked to lymph node metastasis or lymphovascular invasion. These results enhance our comprehension of YAP1's involvement in breast cancer advancement and could influence future targeted treatments.

Acknowledgements

General

The authors express gratitude to the technical personnel of the Anatomical Pathology Laboratory at H Dr. Wahidin Sudirohosodo Hospital and Hasanuddin University Hospital for their support in tissue processing and immunohistochemical staining.

Approval

The Ethics and Research Committee of the Faculty of Medicine at Hasanuddin University in Makassar approved this study (protocol UH24120986).

Conflict of Interest

The authors declare no conflicts of interest.

Ethical Declaration

The research adheres to the Declaration of Helsinki principles, and ethical clearance was secured from the Ethics and Research Committee of the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia, under Approval Number: 1075/UN4.6.4.5.31-/PP36/2024.

Authors Contribution

All authors contributed equally to the article's conception, design, analysis, writing, and editing.

References

1. Rakha E, Martin S, Lee A, Morgan D. The prognostic significance of lymphovascular invasion in invasive breast carcinoma. Cancer. 2012;118(15):3670–80. https://doi.org/10.1002/cncr.26711
2. Rahman M, Mohammed S. Breast cancer metastasis and the lymphatic system (Review. Oncol Lett. 2015;10(3):1233–9. https://doi.org/10.3892/ol.2015.3486
3. Andrade D, Mehta M, Griffith J, Panneerselvam J, Srivastava A, Kim T. YAP1 inhibition radiosensitizes triple negative breast cancer cells by targeting the DNA damage response and cell survival pathways. Oncotarget. 2017;8(58):98495–508. https://doi.org/10.18632/oncotarget.21913
4. Lamar J, Stern P, Liu H, Schindler J, Jiang Z, Hynes R. The Hippo pathway target, YAP, promotes metastasis through its TEAD-interaction domain. Proc Natl Acad Sci U S A. 2012;109(37). https://doi.org/10.1073/pnas.1212021109
5. Shen J, Cao B, Wang Y, Ma C, Zeng Z, Liu L. Hippo component YAP promotes focal adhesion and tumour aggressiveness via transcriptionally activating THBS1/FAK signalling in breast cancer. J Exp Clin Cancer Res. 2018;37(1). https://doi.org/10.1186/s13046-018-0843-8
6. Shen J, Huang Q, Jia W, Feng S, Liu L, Li X, Tao D, Xie D. YAP1 induces invadopodia formation by transcriptionally activating TIAM1 through enhancer in breast cancer. Oncogene. 2022;41(31):3830–45. https://doi.org/10.1038/s41388-022-02344-4
7. Park I, Lee Y, Kim S. YAP1 expression in hormone receptor-positive, HER2-negative breast cancer: correlation with 21-gene signature risk score. Cancers (Basel. 2023;15(20). https://doi.org/10.3390/cancers15205034
8. Liu D, Liang J, Zhang Y, Li X, Wang W, Chen Y. DLAT promotes triple-negative breast cancer progression via a YAP1-dependent pathway. Pathol Res Pract. 2024;254(154398). https://doi.org/10.1016/j.prp.2024.154398
9. Bai X, Li J, Li L, Zhang C, Yang C, Ge J. METTL14 suppresses the expression of YAP1 and the stemness of triple-negative breast cancer. J Exp Clin Cancer Res. 2024;43(1). https://doi.org/10.1186/s13046-024-03225-2
10. Jung O, Pasternak A, Bartosch B. Nuclear phosphoinositide signaling promotes YAP/TAZ-TEAD activation in cancer. EMBO J. 2024;43(13). https://doi.org/10.1038/s44318-024-00085-6
11. Cha Y, Bae S, Kim D, Ahn S, Jeong J, Koo J. High nuclear expression of Yes-associated protein 1 correlates with metastasis in patients with breast cancer. Front Oncol. 2021;11(609743). https://doi.org/10.3389/fonc.2021.609743
12. Li X, Zhuo S, Zhuang T, Cho Y, Wu G, Liu Y. YAP inhibits ERα and ER+ breast cancer growth by disrupting a TEAD–ERα signaling axis. Nat Commun. 2022;13(1). https://doi.org/10.1038/s41467-022-30831-5
13. Luo J, Zou H, Guo Y, Tong T, Chen Y, Xiao Y, Pan Y, Li P. The oncogenic roles and clinical implications of YAP/TAZ in breast cancer. Br J Cancer. 2023;128:1611–24. https://doi.org/10.1038/s41416-023-02182-5
14. Sadri F, Hosseini S, Taheri B. Hippo-YAP/TAZ signaling in breast cancer. Front Oncol. 2023;13(1160911). https://doi.org/10.3389/fonc.2023.1160911
15. Lee S, Go J, Ahn B, Ahn J, Kim J, Park H. Lymphovascular invasion is an independent prognostic factor in breast cancer irrespective of axillary node metastasis and molecular subtypes. Breast Cancer Res Treat. 2023;202(2):399–409. https://doi.org/10.1007/s10549-023-07061-5
16. Asaoka M, Patnaik S, Zhang F, Ishikawa T, Takabe K, Park R. High expression of YAP1 in breast cancer is associated with poor prognosis and response to taxane-based chemotherapy. Breast Cancer Res Treat. 2021;191(2):309–22. https://doi.org/10.1007/s10549-020-05630-5
17. Khalil A, Smits D, Haughton P, Koorman T, Jansen K, Verhagen M. A YAP-centered mechanotransduction loop drives collective breast cancer cell invasion. Nat Commun. 2024;15(1). https://doi.org/10.1038/s41467-024-49230-z
18. Athavale D, Suryawanshi A, Joshi M. The role of Hippo/YAP1 in cancer-associated fibroblasts. Biochim Biophys Acta Rev Cancer. 2024;1879(4). https://doi.org/10.1016/j.bbcan.2024.193012