BUKTI KORESPONDENSI
ARTIKEL JURNAL INTERNASIONAL BEREPUTASI
(Scopus Q4)

Judul	:	**Radiological and Clinicopathological Profiles Between Early- versus Advanced-Stage of Breast Cancer: a Single-Centre Comparative Study**
Jurnal	:	Journal of Neonatal Surgery
Correspondence	:	Shofiyah Latief

No.	Perihal	Tanggal
1	Bukti konfirmasi submit artikel dan artikel yang disubmit	05 Mei 2025
2	Bukti konfirmasi review dan hasil review pertama	08 Mei 2025
3	Bukti konfirmasi submit revisi pertama, respon kepada reviewer, dan artikel yang diresubmit	08 Mei 2025
4	Bukti konfirmasi review dan hasil review kedua	09 Mei 2025
5	Bukti konfirmasi submit revisi kedua, respon kepada reviewer, dan artikel yang diresubmit	09 Mei 2025
6	Bukti konfirmasi artikel *accepted* online	17 Mei 2025
7	Bukti konfirmasi artikel *published* online	17 Mei 2025

1.Bukti konfirmasi submit artikel dan artikel yang disubmit
(05 - 05 - 2025)

A. Bukti konfirmasi artikel berhasil tersubmit

Acceptance Notification Kotak Masuk x

Jneonatalsurg <editor@jneonatalsurg.org>
kepada Shofiyahlatiefumi, saya

02.36 (0 menit yang lalu)

Dear Author,
Shofiyah Latief, Andy Visi Kartika

I am pleased to inform you that we have decided to accept your submission with minor revision. We found your submission,

Radiological and Clinicopathological Profiles Between Early- versus Advanced-Stage of Breast Cancer: a Single-Centre Comparative Study

to meet our expectations, and we do not require that work of this type undergo peer review. We are excited to publish your piece in **Journal of Neonatal Surgery** and we thank you for choosing our journal as a venue for your work.

Your submission is now forthcoming in **Vol. 14 No. 21S (2025)** of **Journal of Neonatal Surgery** and you are welcome to include it in your list of publications. We recognize the hard work that goes into every successful submission and we want to congratulate you on your efforts.

Your submission will now undergo copy editing and formatting to prepare it for publication.

You will shortly receive further instructions.

Best Regards
Editor of **Journal of Neonatal Surgery**

Fariborz Pasha

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LETTER OF ACCE...


INVOICE - SYOFI...

Balas | Balas ke semua | Teruskan | AI Reply

B. Artikel yang tersubmit

Radiological and Clinicopathological Profiles Between Early- versus Advanced-Stage of Breast Cancer: a Single-Centre Comparative Study

Shofiyah Latief[1,*], Andy Visi Kartika[2]

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[2]Pathologic Anatomic Department, Medical Faculty, Universitas Muslim of Indonesia, Makassar
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Introduction

Breast cancer remains a major global health concern for women, ranking among the most prevalent and fatal cancers worldwide. It accounts for approximately 24.5% of all new cancer diagnoses in women, with an annual death toll reaching around 685,000 individuals (1). This pattern is similarly observed in Indonesia, where 65,858 new breast cancer cases and 22,430 deaths were reported in a single year. Notably, about 0.3% of these new cases were identified within the population of South Sulawesi Province (2).

Several key risk factors contribute to the development of breast cancer, including genetic mutations—especially in the BRCA1 and BRCA2 genes—prolonged exposure to estrogen, obesity, and a sedentary lifestyle (3). The likelihood of developing breast cancer increases with age, particularly after 45 years old, with an estimated latency period ranging from 8 to 12 years (4).
The clinical presentation of breast cancer varies widely depending on the stage of the disease. Patients with advanced-stage breast cancer often face significant diagnostic and therapeutic challenges, which also impact their families and caregivers. Diagnosis typically involves a combination of clinical examination, imaging studies, and histopathological evaluation (5). Staging is determined based on the size of the primary tumor (T), involvement of regional lymph nodes (N), and presence of distant metastases (M), all confirmed through histopathological analysis (6,7).

Additionally, immunohistochemistry plays a crucial role in identifying molecular subtypes, assessing prognosis, and guiding treatment decisions (8). Research indicates that advanced breast cancer patients are more likely to exhibit higher histological grades (III and IV) and overexpress HER2, a marker associated with more aggressive disease (9). For instance, Alqahtani et al. (2020) reported that advanced-stage patients in Saudi Arabia commonly presented with tumors larger than 5 cm and more frequent lymph node involvement compared to early-stage patients. Similarly, Wahidin et al. (2019) found that the luminal B subtype predominates among advanced breast cancer cases in Indonesia.

Despite the importance of this information for tailoring diagnostic and therapeutic approaches, there remains a lack of comprehensive data from Ibnu Sina Hospital comparing the clinical, radiological, and histopathological features of early versus advanced breast cancer. Such data are essential to develop more precise and locally relevant management protocols.

Method

Our study used a quantitative approach with a descriptive correlational and a cross-sectional designs to evaluate the clinical, radiological, and histopathological variations between early- and

advanced-stage breast cancer patients treated at IBNU SINA HOSPITAL MAKASSAR. All information was gathered in a single observation. Simple random sampling technique was carried out. Radiological and clinicopathological findings were gathered by reviewing 40 medical records derived from female patients who fulfilled the criteria.

Clinical variable assessed were age, lymph node involvement, and the presence of distant metastatic. Tumour diameter, lymph node enlargement, and tumour mass localisation measured radiologically were gathered. While histopathological characteristics include tumour gros and microscopic feature, such as tumor type and morphology, degree of cell differentiation (grading), surgical margin involvement, lymphovascular invasion, hormonal receptor status (oestrogen and progesterone), HER2 status, and proliferation index (Ki-67). This study was conducted according to ethical board approval from Medical Faculty, Universitas Muslim of Indonesia, Makassar.

Results

This study reviewed 40 medical records of breast cancer patients. They were divided into two groups, early and advanced breast cancer, consisting of 20 individual. Their clinical features are shown in Table 1. The average age of patients with early-stage breast cancer is 45 y.o. No lymph node enlargement nor distant metastases were found. Unlike the group with an advanced stage. They were approximately 58 y.o. on average. Enlarged lymph nodes were detected in 14 patients and 10 of them were accompanied with distant metastasis.

Table 1. Clinical Features of Breast Cancer Patients

Characteristic	Early Stage (n=20)	Late Stage (n=20)
Age (average)	45 y.o	58 y.o
Lymph node involvement	none	14
Distant metastatic	none	10

The Ultrasonography profiles were displayed in Table 2. Patients with early-stage breast cancer typically have solid lumps that are regular, round, or oval in shape with an average size of 1.5 cm. There are few internal echo regions and poor echogenicity (hypoechoic) at the lesion margins, which seem obvious. Vascularization was found to be very low or absent by Doppler testing. There were either no calcification structures or very little. Neither the breast walls nor lymph nodes were affected.

Table 2. Ultrasonography (USG) Findings of Breast Cancer Patients

Characteristic	Early Stage (n=20)	Late Stage (n=20)
Tumor Type	Solid	Solid
Tumor Size (average)	1,5 cm	4 cm
Tumor Shape	Regular (round to oval)	Irregular (abnormal)
Tumor Margin	Obvious	Indistinct
Echogenicity	Hypoechoic, with small echo area	Homogen, severe hypoechoic, with necrosis area

Characteristic	Early Stage (n=20)	Late Stage (n=20)
Vascularization (Doppler)	None or little	Hypervascular with observed neovascularization
Tumor Calcification	None or little	Micro- or Macrocalcification
Regional Lymph Node Enlargement	None	Detected
Breast Wall Infiltration	None	Clearly observed

In contrast, the advanced stage patient group exhibited bigger tumour sizes, reaching an average of 4 cm and exhibiting infiltrative qualities, leading the lesion boundaries to be hazy and unclear, with an uneven and aberrant shape. Although the lesion looks uniform, it is extremely hypoechoic and has necrotic patches. Doppler examination can be used to assess increased vascularization, which is typically accompanied by neovascularisation. Large calcifications and/or microcalcifications are noticeable and simple to identify. Most patients have radiological involvement of regional lymph nodes and plainly apparent infiltration into the breast wall.

In contrary, the patient of advanced stage group were had larger tumour size, reaching an average of 4 cm and showing infiltrative properties. Causing the lesion boundaries to be blurred and unclear, with an irregular and abnormal shape. The lesion appears homogeneous but very hypoechoic and accompanied by areas of necrosis. Increased vascularization, mostly accompanied by neovascularization, can be evaluated using Doppler examination. Microcalcifications and/or large calcifications appear prominent and easily recognized. Radiological involvement of regional lymph nodes is seen in most patients, as is infiltration into the breast wall which is clearly visible.

Table 3. Tumor Gros and Microscopic Identification of Breast Cancer Patients

Characteristic	Early Stage (n=20)	Late Stage (n=20)
Tumor localization	Single 16	Multifocal 12
Diameter	Small (< 1,5 cm): 16 (average 1.5 cm)	Big (> 5 cm): 18 (average 6.2 cm)
Consistency	Firm 17	Solid 16
Cell Proliferation	Low 18	High 14
Tumor type Ductal invasive	12	18
Tumor Diferensiation	Well differentiated 14	Poorly differentiated 15
Tumor grade	Intermediate grade: 15	Intermediate grade: 18
Hormonal receptor status positive	18	8
HER2 status positive	5	12
Ki-67 indeks	Low: 18	High: 14
Lymph node involvement	4	16
Limfovaskular invasion	2/	12
Distant Metastasis	0	10

Surgical margin involvement positive	1	9

Table 2 shows the histopathological analysis of tumour tissue from both patient groups. The average age of patients with early stage breast cancer was 45 years, whereas the advanced stage group had an older age of 58 years. These study groups consisted entirely of female participants. Morphologically, tumours in the early stage were smaller, with 16 of 20 patients having a diameter of less than 2 cm, but in the late stage, 18 patients had a tumour mass of more than 5 cm.

The most common histological type in both groups was invasive ductal carcinoma. However, there were considerable disparities in the level of cell differentiation. In the early stage, the majority of tumours showed high differentiation (14/20 individuals), but in the advanced stage, 15 patients had low differentiation.

Hormonal receptor status revealed that oestrogen and progesterone hormone receptor expression was more common in early stage patients (18/20) versus just 8 patients in advanced stages. In contrast, HER2 overexpression was more common in the advanced stage group (12/20 patients).

The Ki-67 index was used to measure the rate of cell proliferation. The advanced stage group had the highest index (14/20), while the early stage group had a low proliferation index (12/20 individuals).

Lymphatic system involvement, including regional lymph node enlargement, was also more common in the late stage, with 16 and 14 patients, respectively, compared to 4 and 0 cases in the early stage. Lympho-vascular invasion and good surgical margins were also more common among the advanced patients.

The average tumour diameter in advanced stages was 6.2 cm, which was significantly larger than the early stage average of 1.5 cm. Furthermore, advanced stage patients tended to have solid, multifocal tumours (16/20 patients) with considerable proliferative activity (grade 3). Early-stage tumours, on the other hand, were typically non-solid, solitary, and localised (16/20 patients).

Discussion

Radiological and Clinicopathological Differences Between Early and Advanced Breast Cancer Stages

This comparative study conducted at a single center offers important insights into the distinct radiological and clinicopathological characteristics that separate early-stage breast cancer from advanced-stage disease. The results reveal significant differences across various parameters, which could improve diagnostic precision and guide treatment planning.

Clinical Presentation and Symptoms

The clinical features of early versus advanced breast cancer show marked differences. Early-stage breast cancer often presents with few or no symptoms and is frequently detected through routine screening or physical exams. These tumors tend to be small, painless, and cause minimal

changes in breast appearance. Conversely, advanced breast cancer is characterized by more obvious and severe symptoms, making it easier to identify clinically.

The age difference observed—early-stage patients averaging 45 years old and late-stage patients averaging 58 years—is consistent with previous studies. For example, Lodi et al. (2021) found that older patients are more likely to present with advanced disease, possibly due to lower screening rates and distinct tumor biology in postmenopausal women. This age gap may also reflect differences in tumor aggressiveness and growth patterns between pre- and postmenopausal breast cancer.

The high rates of lymph node involvement (70%) and distant metastasis (50%) in advanced cases align with the natural course of breast cancer progression. These findings support Ibrahim et al. (2022), who reported lymph node metastasis in 65-75% of advanced breast cancer patients, significantly influencing prognosis and treatment choices.

Radiological Characteristics

Imaging studies such as mammography and ultrasonography in early-stage breast cancer typically show small, solid masses with features common to various tumor types. Microcalcifications and metastatic signs are rarely seen at this stage. In contrast, advanced tumors are more conspicuous on imaging, with detectable spread to lymph nodes or distant organs like the lungs and liver via CT or PET scans.

Ultrasonography revealed notable differences between early and advanced disease. The average tumor size was 1.5 cm in early-stage versus 4 cm in advanced-stage cases, a critical diagnostic factor. Nakano et al. (2020) demonstrated a strong correlation between tumor size and disease stage, with each additional centimeter linked to about a 10% decrease in 5-year survival.

Tumor shape also changes with progression: early-stage tumors tend to be round or oval with clear margins, while advanced tumors show irregular shapes and poorly defined edges, indicating greater invasiveness. Li et al. (2023) found that irregular margins increase the risk of local invasion and lymph node metastasis by 3.4 times.

Advanced tumors also exhibit distinct vascular patterns, including neovascularization, consistent with Wang et al. (2019), who identified angiogenesis as a marker of aggressive breast cancer subtypes. The presence of calcifications and breast wall infiltration in late-stage disease further underscores the value of detailed ultrasonographic evaluation.

Ultrasonography remains a vital, non-invasive tool for initial breast cancer assessment and staging. The significant imaging differences observed likely reflect tumor morphological changes as the disease advances, providing important clinical and pathological insights.

Histopathological Findings

Histopathology of early-stage breast cancer often shows ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), with tumors confined and not invading surrounding tissues. These tumors are usually small, low-grade, and show minimal vascular invasion.

In contrast, late-stage tumors frequently present as multifocal (60% of cases), compared to predominantly single lesions (80%) in early disease, indicating a tendency for advanced cancer to spread within the breast. This pattern aligns with Martelli et al. (2021), who linked multifocality to higher recurrence and worse prognosis.

Cell proliferation rates differ markedly, with low proliferation in 90% of early cases versus high proliferation in 70% of advanced cases, reflecting more aggressive tumor biology. Differentiation patterns also shift, with well-differentiated tumors common in early stages (70%) and poorly differentiated tumors predominating in late stages (75%). Rahman et al. (2022) showed that poorly differentiated tumors have greater genomic instability and resistance to therapy.

Advanced tumors demonstrate increased aggressiveness, including more frequent vascular invasion and potential for distant metastasis. Hormone receptor status also changes, with advanced cancers often being hormone receptor-negative or HER2-positive, indicating more aggressive disease.

Molecular Subtypes and Biomarkers

Molecular profiling reveals important differences with therapeutic implications. Hormone receptor positivity drops dramatically from 90% in early-stage to 40% in advanced-stage disease, possibly reflecting selection for hormone-independent tumor cells or different subtypes. Conversely, HER2 positivity rises from 25% in early to 60% in late-stage cases, consistent with Zhu et al. (2020), who reported that HER2-enriched tumors tend to be more advanced and aggressive.

The Ki-67 proliferation index shifts from predominantly low in early disease (90%) to high in advanced cases (70%). Yerushalmi et al. (2021) found that high Ki-67 is strongly associated with poorer disease-free and overall survival, making it a key prognostic marker.

Study Limitations Despite its contributions, this study has limitations. The small sample size (40 patients) limits statistical power and may not represent the full diversity of breast cancer. Being a single-center study at Ibnu Sina Hospital restricts generalizability to other populations and healthcare settings.

The cross-sectional design prevents tracking disease progression within individuals, limiting causal inferences between early and late-stage features. Important factors such as comorbidities, socioeconomic status, and screening history were not included, which could affect disease presentation.

The study also lacks advanced molecular profiling beyond basic receptor status, limiting deeper understanding of biological mechanisms. Additionally, treatment outcomes and long-term follow-up data are absent, reducing clinical applicability.

Conclusion

This study highlights clear radiological and clinicopathological differences between early and advanced breast cancer stages. At Ibnu Sina Hospital, recognizing these distinctions is essential for optimizing diagnosis and treatment strategies. The findings underscore the importance of early detection and thorough evaluation in breast cancer care. Future research with larger, multicenter cohorts, longitudinal follow-up, and comprehensive molecular analysis will further clarify breast cancer progression and may identify novel therapeutic targets.

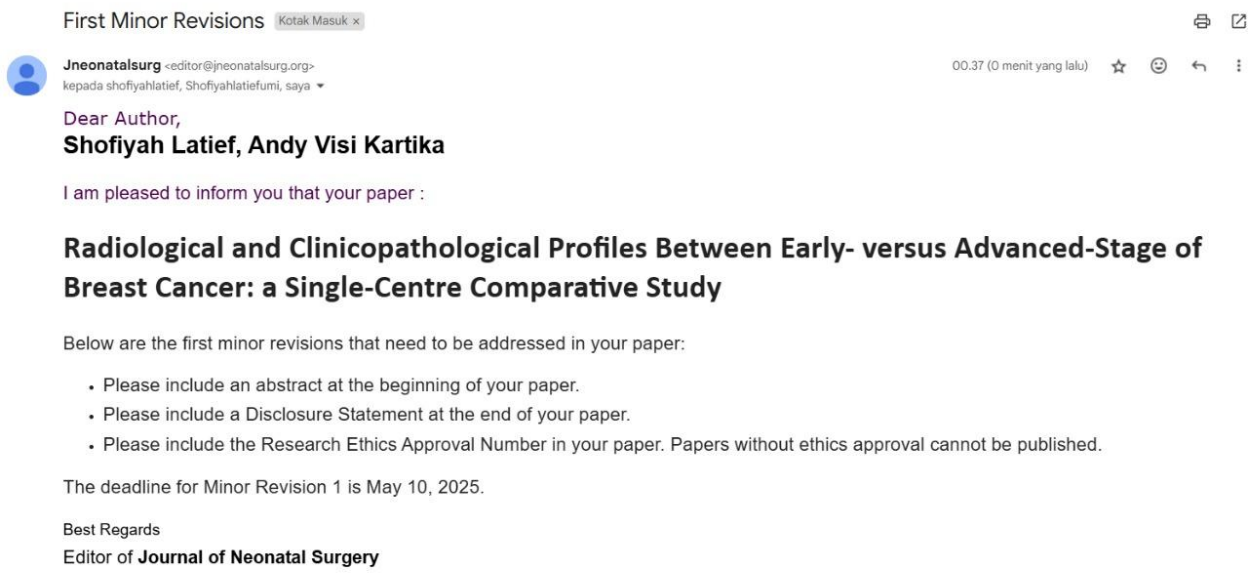
References

1. Global Cancer Observatory (Globocan). Lyon: International Agency for Research on Cancer; 2022.
2. Kemenkes RI. Data Kanker Payudara di Indonesia. Jakarta: Kementerian Kesehatan Republik Indonesia; 2023.
3. World Health Organization. Breast Cancer Fact Sheet [Internet]. Geneva: WHO; 2023 [cited 2025 Apr 27]. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer
4. Fadi MA, Troy F. Breast Cancer. Baghdad: Iraqia University, Michigan State University: National Library Of Medicine; 2022.
5. Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Diagnostic Accuracy of Mammography, Clinical Examination, US, and MR Imaging in Preoperative Assessment of Breast Cancer. Radiology. 2012;265(1):45-56.
6. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al, editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
7. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99.
8. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus. Ann Oncol. 2013;24(9):2206-2223.
9. Alqahtani MS, Alshbrige AA, Alkhamshi AM, Alkenani NA, Alshammari KF, Sirwi A, et al. Molecular subtypes of breast cancer: current role in diagnosis, prognosis and therapy. Pathophysiology. 2020;27(4):100565.
10. Wahidin M, Djuwita R, Adisasmita A. Oral contraceptive and breast cancer risks: a case control study in six referral hospitals in Indonesia. Asian Pac J Cancer Prev. 2019;20(8):2389-2395.

11. Lodi M, Scheer L, Reix N, Heitz D, Carin AJ, Thiébaut N, et al. Breast cancer in elderly women and altered clinico-pathological characteristics: a systematic review. Breast Cancer Res Treat. 2021;166(3):657-68.
12. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2022;2022:437971.
13. Nakano S, Otsuka M, Mibu A, Oinuma T. Significance of high-resolution ultrasound in the early detection of breast cancer: correlation between tumor size and prognostic factors. Ultrasound Med Biol. 2020;46(3):642-50.
14. Li Y, Chen J, Zhu Y, Zhou S, Xu Y, Wang X. Ultrasound features of breast cancer: association with tumor characteristics and molecular subtypes. Eur Radiol. 2023;33(1):119-29.
15. Wang L, Zhang F, Wu J, Xu N, Zhao Y. Quantitative assessment of tumor vascularity by contrast-enhanced ultrasound: correlation with prognostic markers in breast cancer. Eur J Radiol. 2019;118:241-8.
16. Martelli G, Miceli R, Folli S, Guzzetti E, Chifu C, Maugeri I, et al. Prognostic factors for distant recurrence in patients with multifocal-multicentric breast cancer. Breast Cancer Res Treat. 2021;189(3):851-8.
17. Rahman M, Mohammed S, Khan MA, Zaman MH. Mechanobiology of tumor cell differentiation in breast cancer and its clinical implications. Cell Mol Bioeng. 2022;15(1):21-34.
18. Zhu X, Chen L, Liu L, Niu X. HER2-positive breast cancer is associated with an increased risk of positive margins after initial lumpectomy: a retrospective analysis. World J Surg Oncol. 2020;18(1):228.
19. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol. 2021;22(3):e100-10.
20. Callari M, Cappelletti V, D'Aiuto F, Musella V, Lembo A, Petel F, et al. Subtype-specific metagene-based prediction of outcome after neoadjuvant and adjuvant treatment in breast cancer. Clin Cancer Res. 2020;26(1):83-95.
21. Araki K, Ito Y, Fukada I, Kobayashi K, Miyagawa Y, Imamura M, et al. Predictive impact of absolute lymphocyte counts for progression-free survival in human epidermal growth factor receptor 2-positive advanced breast cancer treated with pertuzumab and trastuzumab plus eribulin or nab-paclitaxel. BMC Cancer. 2021;21(1):287.
22. Jia M, Gao X, Zhang Y, Hoffmeister M, Brenner H. Different definitions of CpG island methylator phenotype and outcomes of colorectal cancer: a systematic review. Clin Epigenetics. 2019;11(1):103.
23. Xie Y, Liu L, Gong G, Tang S, Wang Z, Jiang M, et al. Comparative proteomic analysis of breast cancer revealed altered expression of key proteins related to lymph node metastasis. Proteomics Clin Appl. 2022;16(1):2100051.
24. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med. 2023;379(20):1926-36.
25. Singh K, Tantry US, Lin L, Gesheff MG, Jakubowski J, Tomaszewski M, et al. Delayed and attenuated platelet inhibition response in patients with metabolic syndrome after moderate clopidogrel dose while undergoing percutaneous coronary intervention and relationship to resistin levels. Am J Cardiol. 2020;115(10):1380-6.

2.Konfirmasi review dan hasil review pertama (08-05-2025)

A. Tangkapan Layar Notifikasi Hasil Review



First Minor Revisions Kotak Masuk ×

Jneonatalsurg <editor@jneonatalsurg.org>
kepada shofiyahlatief, Shofiyahlatiefumi, saya

00.37 (0 menit yang lalu)

Dear Author,
Shofiyah Latief, Andy Visi Kartika

I am pleased to inform you that your paper :

Radiological and Clinicopathological Profiles Between Early- versus Advanced-Stage of Breast Cancer: a Single-Centre Comparative Study

Below are the first minor revisions that need to be addressed in your paper:

- Please include an abstract at the beginning of your paper.
- Please include a Disclosure Statement at the end of your paper.
- Please include the Research Ethics Approval Number in your paper. Papers without ethics approval cannot be published.

The deadline for Minor Revision 1 is May 10, 2025.

Best Regards
Editor of **Journal of Neonatal Surgery**

B. Hasil review pertama

Dear Author,
Shofiyah Latief, Andy Visi Kartika

I am pleased to inform you that your paper :

Radiological and Clinicopathological Profiles Between Early- versus Advanced-Stage of Breast Cancer: a Single-Centre Comparative Study

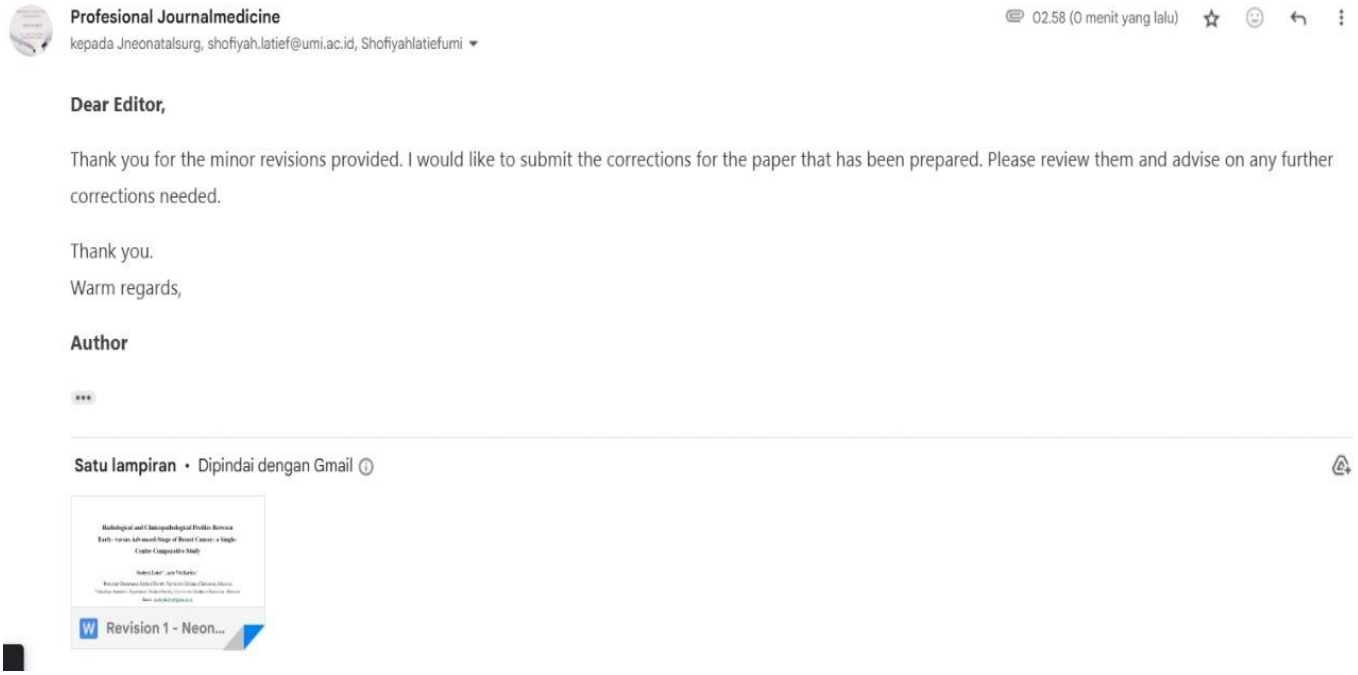
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The deadline for Minor Revision 1 is May 10, 2025.
Best Regards
Editor of **Journal of Neonatal Surgery**

3. Konfirmasi submit revisi pertama, respon Kepada reviewer, dan artikel yang diresubmit (08-05-2025)

A. Cover letter review, respon Kepada reviewer



Profesional Journalmedicine
kepada Jneonatalsurg, shofiyah.latief@umi.ac.id, Shofiyahlatiefumi

02.58 (0 menit yang lalu)

Dear Editor,

Thank you for the minor revisions provided. I would like to submit the corrections for the paper that has been prepared. Please review them and advise on any further corrections needed.

Thank you.
Warm regards,

Author

Satu lampiran • Dipindai dengan Gmail

Revision 1 - Neon...

B. Artikel yang diresubmit

Radiological and Clinicopathological Profiles Between Early- versus Advanced-Stage of Breast Cancer: a Single-Centre Comparative Study

Shofiyah Latief [1,*], Andy Visi Kartika [2]

[1] Radiology Department, Medical Faculty, Universitas Muslim of Indonesia, Makassar,
[2] Pathologic Anatomic Department, Medical Faculty, Universitas Muslim of Indonesia, Makassar
Email: shofiyah.latief@umi.ac.id

Abstract

Introduction: Breast cancer remains a leading cause of morbidity and mortality among women worldwide, with significant clinical and pathological differences between early and advanced stages. Understanding these differences is crucial for improving diagnosis and treatment strategies.

Methods: This cross-sectional, descriptive correlational study reviewed 40 medical records of female breast cancer patients treated at Ibnu Sina Hospital, Makassar. Patients were divided into early-stage (n=20) and advanced-stage (n=20) groups. Clinical, radiological, and histopathological data were collected, including tumor size, lymph node involvement, hormone receptor status, HER2 expression, and proliferation index (Ki-67).

Results: The average age was 45 years in early-stage and 58 years in advanced-stage patients. Early-stage tumors were smaller (average 1.5 cm), well-differentiated, hormone receptor-positive, and showed low Ki-67 proliferation. Advanced-stage tumors were larger (average 4-6.2 cm), poorly differentiated, with higher HER2 positivity, increased lymph node involvement, distant metastasis, and higher Ki-67 index. Radiologically, early tumors appeared as regular, hypoechoic masses with clear margins, while advanced tumors showed irregular shapes, necrosis, neovascularization, calcifications, and breast wall infiltration.

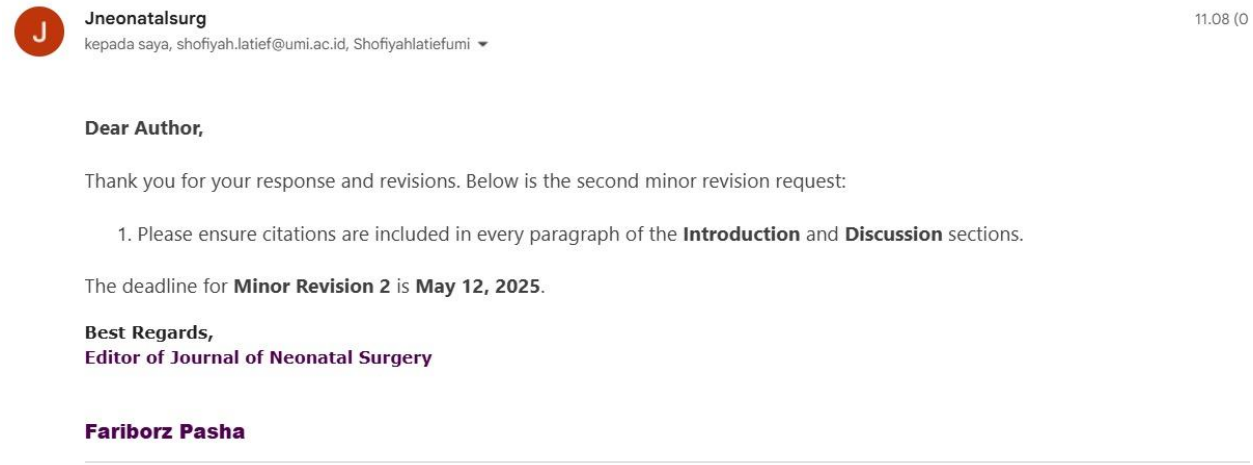
Discussion: Significant radiological and clinicopathological differences exist between early and advanced breast cancer stages, reflecting tumor aggressiveness and progression. These findings align with previous studies emphasizing the importance of early detection and tailored treatment.

Disclosure Statement

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Ethical Approval : This study was approved by the Research Ethics Committee of the Muslim University of Indonesia with Number: 213/A.1/KEP-UMI/VI/2024
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication.

4.Konfirmasi review dan hasil review kedua (09-05-2025)

C. Tangkapan Layar Notifikasi Hasil Review



Jneonatalsurg 11.08 (0
kepada saya, shofiyah.latief@umi.ac.id, Shofiyahlatiefumi

Dear Author,

Thank you for your response and revisions. Below is the second minor revision request:

1. Please ensure citations are included in every paragraph of the **Introduction** and **Discussion** sections.

The deadline for **Minor Revision 2** is **May 12, 2025**.

Best Regards,
Editor of Journal of Neonatal Surgery

Fariborz Pasha

D. Hasil review kedua

Dear Author,
Thank you for your response and revisions. Below is the second minor revision request:

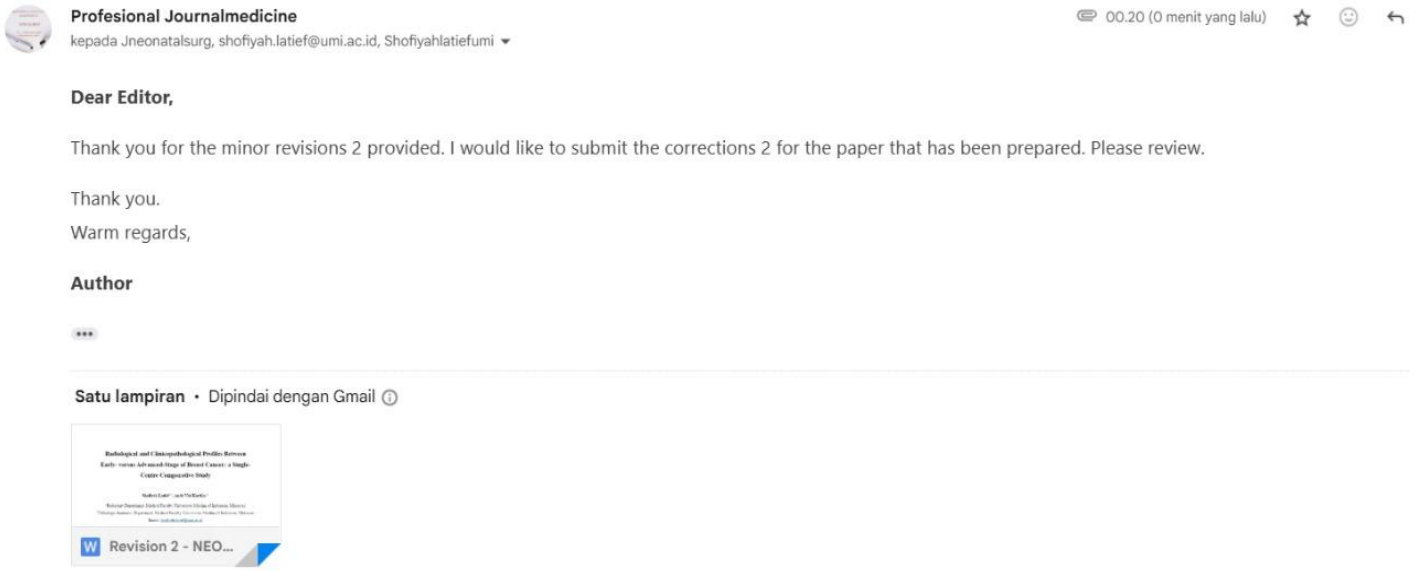
1. Please ensure citations are included in every paragraph of the **Introduction** and **Discussion** sections.

The deadline for **Minor Revision 2** is **May 12, 2025**.
Best Regards,
Editor of Journal of Neonatal Surgery

Fariborz Pasha

5.Konfirmasi submit revisi kedua, respon kepada reviewer, dan artikel yang diresubmit (09-05-2025)

A. Cover letter review, respon Kepada reviewer



Profesional Journalmedicine
kepada Jneonatalsurg, shofiyah.latief@umi.ac.id, Shofiyahlatiefumi

00.20 (0 menit yang lalu)

Dear Editor,

Thank you for the minor revisions 2 provided. I would like to submit the corrections 2 for the paper that has been prepared. Please review.

Thank you.
Warm regards,

Author

•••

Satu lampiran • Dipindai dengan Gmail

Revision 2 - NEO...

B. Artikel yang diresubmit

Introduction

Breast cancer remains a major global health concern for women, ranking among the most prevalent and fatal cancers worldwide. It accounts for approximately 24.5% of all new cancer diagnoses in women, with an annual death toll reaching around 685,000 individuals [1]. This pattern is similarly observed in Indonesia, where 65,858 new breast cancer cases and 22,430 deaths were reported in a single year. Notably, about 0.3% of these new cases were identified within the population of South Sulawesi Province [2].

Several key risk factors contribute to the development of breast cancer, including genetic mutations—especially in the BRCA1 and BRCA2 genes—prolonged exposure to estrogen, obesity, and a sedentary lifestyle [3]. The likelihood of developing breast cancer increases with age, particularly after 45 years old, with an estimated latency period ranging from 8 to 12 years [4].

The clinical presentation of breast cancer varies widely depending on the stage of the disease. Patients with advanced-stage breast cancer often face significant diagnostic and therapeutic challenges, which also impact their families and caregivers [5]. Diagnosis typically involves a combination of clinical examination, imaging studies, and histopathological evaluation [6]. Staging is determined based on the size of the primary tumor (T), involvement of regional lymph nodes (N), and presence of distant metastases (M), all confirmed through histopathological analysis [7,8].

Additionally, immunohistochemistry plays a crucial role in identifying molecular subtypes, assessing prognosis, and guiding treatment decisions [9]. Research indicates that advanced breast cancer patients are more likely to exhibit higher histological grades (III and IV) and overexpress HER2, a marker associated with more aggressive disease [10]. For instance, Alqahtani [10] reported that advanced-stage patients in Saudi Arabia commonly presented with tumors larger than 5 cm and more frequent lymph node involvement compared to early-stage patients. Similarly, Wahidin

Discussion

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This comparative study conducted at a single center offers important insights into the distinct radiological and clinicopathological characteristics that separate early-stage breast cancer from advanced-stage disease. The results reveal significant differences across various parameters, which could improve diagnostic precision and guide treatment planning.

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The high rates of lymph node involvement (70%) and distant metastasis (50%) in advanced cases align with the natural course of breast cancer progression. These findings support Ibrahim [13], who reported lymph node metastasis in 65-75% of advanced breast cancer patients, significantly influencing prognosis and treatment choices.

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Ultrasonography revealed notable differences between early and advanced disease. The average tumor size was 1.5 cm in early-stage versus 4 cm in advanced-stage cases, a critical diagnostic factor. Nakano [14] demonstrated a strong correlation between tumor size and disease stage, with each additional centimeter linked to about a 10% decrease in 5-year survival.

Tumor shape also changes with progression: early-stage tumors tend to be round or oval with clear margins, while advanced tumors show irregular shapes and poorly defined edges, indicating greater invasiveness. Li [15] found that irregular margins increase the risk of local invasion and lymph node metastasis by 3.4 times.

Advanced tumors also exhibit distinct vascular patterns, including neovascularization, consistent with Wang [16], who identified angiogenesis as a marker of aggressive breast cancer subtypes. The presence of calcifications and breast wall infiltration in late-stage disease further underscores the value of detailed ultrasonographic evaluation.

Ultrasonography remains a vital, non-invasive tool for initial breast cancer assessment and staging. The significant imaging differences observed likely reflect tumor morphological changes as the disease advances, providing important clinical and pathological insights.

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Histopathology of early-stage breast cancer often shows ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), with tumors confined and not invading surrounding tissues. These tumors are usually small, low-grade, and show minimal vascular invasion [17].

In contrast, late-stage tumors frequently present as multifocal (60% of cases), compared to predominantly single lesions (80%) in early disease, indicating a tendency for advanced cancer to spread within the breast. This pattern aligns with Martelli [18], who linked multifocality to higher recurrence and worse prognosis.

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Advanced tumors demonstrate increased aggressiveness, including more frequent vascular invasion and potential for distant metastasis [20,21]. Hormone receptor status also changes, with advanced cancers often being hormone receptor-negative or HER2-positive, indicating more aggressive disease [22,23].

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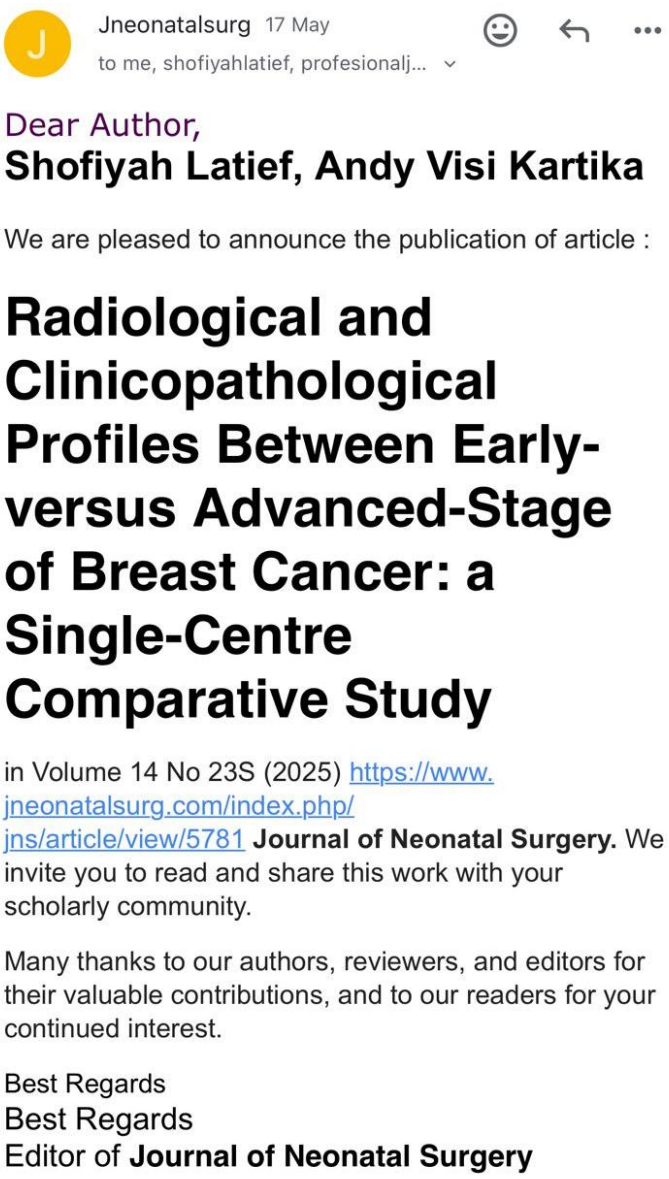
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Radiological and Clinicopathological Profiles Between Early- versus Advanced-Stage of Breast Cancer: a Single-Centre Comparative Study

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ABSTRACT

Introduction: Breast cancer remains a leading cause of morbidity and mortality among women worldwide, with significant clinical and pathological differences between early and advanced stages. Understanding these differences is crucial for improving diagnosis and treatment strategies.

Methods: This cross-sectional, descriptive correlational study reviewed 40 medical records of female breast cancer patients treated at Ibnu Sina Hospital, Makassar. Patients were divided into early-stage (n=20) and advanced-stage (n=20) groups. Clinical, radiological, and histopathological data were collected, including tumor size, lymph node involvement, hormone receptor status, HER2 expression, and proliferation index (Ki-67).

Results: The average age was 45 years in early-stage and 58 years in advanced-stage patients. Early-stage tumors were smaller (average 1.5 cm), well-differentiated, hormone receptor-positive, and showed low Ki-67 proliferation. Advanced-stage tumors were larger (average 4-6.2 cm), poorly differentiated, with higher HER2 positivity, increased lymph node involvement, distant metastasis, and higher Ki-67 index. Radiologically, early tumors appeared as regular, hypoechoic masses with clear margins, while advanced tumors showed irregular shapes, necrosis, neovascularization, calcifications, and breast wall infiltration.

Discussion: Significant radiological and clinicopathological differences exist between early and advanced breast cancer stages, reflecting tumor aggressiveness and progression. These findings align with previous studies emphasizing the importance of early detection and tailored treatment.

Conclusion: Recognizing distinct features of early versus advanced breast cancer is essential for optimizing patient management. Further multicenter studies with larger cohorts are recommended to enhance understanding and improve outcomes.

Keywords: *Breast cancer, early stage, advanced stage, radiology, histopathology, hormone receptor, HER2, Ki-67.*

1. INTRODUCTION

Breast cancer remains a major global health concern for women, ranking among the most prevalent and fatal cancers worldwide. It accounts for approximately 24.5% of all new cancer diagnoses in women, with an annual death toll reaching around 685,000 individuals [1]. This pattern is similarly observed in Indonesia, where 65,858 new breast cancer cases and 22,430 deaths were reported in a single year. Notably, about 0.3% of these new cases were identified within the population of South Sulawesi Province [2].

Several key risk factors contribute to the development of breast cancer, including genetic mutations—especially in the BRCA1 and BRCA2 genes—prolonged exposure to estrogen, obesity, and a sedentary lifestyle [3]. The likelihood of developing breast cancer increases with age, particularly after 45 years old, with an estimated latency period ranging from 8 to 12 years [4].

The clinical presentation of breast cancer varies widely depending on the stage of the disease. Patients with advanced-stage breast cancer often face significant diagnostic and therapeutic challenges, which also impact their families and caregivers [5]. Diagnosis typically involves a combination of clinical examination, imaging studies, and histopathological evaluation [6]. Staging is determined based on the size of the primary tumor (T), involvement of regional lymph nodes (N), and presence of distant metastases (M), all confirmed through histopathological analysis [7,8].

Additionally, immunohistochemistry plays a crucial role in identifying molecular subtypes, assessing prognosis, and guiding treatment decisions [9]. Research indicates that advanced breast cancer patients are more likely to exhibit higher histological grades (III and IV) and overexpress HER2, a marker associated with more aggressive disease [10]. For instance, Alqahtani [10] reported that advanced-stage patients in Saudi Arabia commonly presented with tumors larger than 5 cm and more frequent lymph node involvement compared to early-stage patients. Similarly, Wahidin [11] found that the luminal B subtype predominates among advanced breast cancer cases in Indonesia.

Despite the importance of this information for tailoring diagnostic and therapeutic approaches, there remains a lack of comprehensive data from Ibnu Sina Hospital comparing the clinical, radiological, and histopathological features of early versus advanced breast cancer. Such data are essential to develop more precise and locally relevant management protocols.

2. METHOD

Our study used a quantitative approach with a descriptive correlational and a cross-sectional designs to evaluate the clinical, radiological, and histopathological variations between early- and advanced-stage breast cancer patients treated at IBNU SINA HOSPITAL MAKASSAR. All information was gathered in a single observation. Simple random sampling technique was carried out. Radiological and clinicopathological findings were gathered by reviewing 40 medical records derived from female patients who fulfilled the criteria.

Clinical variable assessed were age, lymph node involvement, and the presence of distant metastatic. Tumour diameter, lymph node enlargement, and tumour mass localisation measured radiologically were gathered. While histopathological characteristics include tumour gros and microscopic feature, such as tumor type and morphology, degree of cell differentiation (grading), surgical margin involvement, lymphovascular invasion, hormonal receptor status (oestrogen and progesterone), HER2 status, and proliferation index (Ki-67). This study was conducted according to ethical board approval from Medical Faculty, Universitas Muslim of Indonesia, Makassar.

3. RESULTS

This study reviewed 40 medical records of breast cancer patients. They were divided into two groups, early and advanced breast cancer, consisting of 20 individual. Their clinical features are shown in Table 1. The average age of patients with early-stage breast cancer is 45 y.o. No lymph node enlargement nor distant metastases were found. Unlike the group with an advanced stage. They were approximately 58 y.o. on average. Enlarged lymph nodes were detected in 14 patients and 10 of them were accompanied with distant metastasis.

Table 1. Clinical Features of Breast Cancer Patients

Characteristic	Early Stage (n=20)	Late Stage (n=20)
Age (average)	45 y.o	58 y.o
Lymph node involvement	none	14
Distant metastatic	none	10

The Ultrasonography profiles were displayed in Table 2. Patients with early-stage breast cancer typically have solid lumps that are regular, round, or oval in shape with an average size of 1.5 cm. There are few internal echo regions and poor echogenicity (hypoechoic) at the lesion margins, which seem obvious. Vascularization was found to be very low or absent by Doppler testing. There were either no calcification structures or very little. Neither the breast walls nor lymph nodes were affected.

Table 2. Ultrasonography (USG) Findings of Breast Cancer Patients

Characteristic	Early Stage (n=20)	Late Stage (n=20)
Tumor Type	Solid	Solid
Tumor Size (average)	1,5 cm	4 cm
Tumor Shape	Regular (round to oval)	Irregular (abnormal)
Tumor Margin	Obvious	Indistinct
Echogenicity	Hypoechoic, with small echo area	Homogen, severe hypoechoic, with

Characteristic	Early Stage (n=20)	Late Stage (n=20)
		necrosis area
Vascularization (Doppler)	None or little	Hypervascular with observed neovascularization
Tumor Calcification	None or little	Micro- or Macrocalcification
Regional Lymph Node Enlargement	None	Detected
Breast Wall Infiltration	None	Clearly observed

In contrast, the advanced stage patient group exhibited bigger tumour sizes, reaching an average of 4 cm and exhibiting infiltrative qualities, leading the lesion boundaries to be hazy and unclear, with an uneven and aberrant shape. Although the lesion looks uniform, it is extremely hypoechoic and has necrotic patches. Doppler examination can be used to assess increased vascularization, which is typically accompanied by neovascularisation. Large calcifications and/or microcalcifications are noticeable and simple to identify. Most patients have radiological involvement of regional lymph nodes and plainly apparent infiltration into the breast wall.

In contrary, the patient of advanced stage group were had larger tumour size, reaching an average of 4 cm and showing infiltrative properties. Causing the lesion boundaries to be blurred and unclear, with an irregular and abnormal shape. The lesion appears homogeneous but very hypoechoic and accompanied by areas of necrosis. Increased vascularization, mostly accompanied by neovascularization, can be evaluated using Doppler examination. Microcalcifications and/or large calcifications appear prominent and easily recognized. Radiological involvement of regional lymph nodes is seen in most patients, as is infiltration into the breast wall which is clearly visible.

Table 3. Tumor Gros and Microscopic Identification of Breast Cancer Patients

Characteristic	Early Stage (n=20)	Late Stage (n=20)
Tumor localization	Single 16	Multifocal 12
Diameter	Small (< 1,5 cm): 16 (average 1.5 cm)	Big (> 5 cm): 18 (average 6.2 cm)
Consistency	Firm 17	Solid 16
Cell Proliferation	Low 18	High 14
Tumor type Ductal invasive	12	18
Tumor Diferensiation	Well differentiated 14	Poorly differentiated 15
Tumor grade	Intermediate grade: 15	Intermediate grade: 18
Hormonal receptor status positive	18	8
HER2 status positive	5	12
Ki-67 indeks	Low: 18	High: 14
Lymph node involvement	4	16
Limfovaskular invasion	2	12
Distant Metastasis	0	10
Surgical margin involvement positive	1	9

Table 2 shows the histopathological analysis of tumour tissue from both patient groups. The average age of patients with early stage breast cancer was 45 years, whereas the advanced stage group had an older age of 58 years. These study groups consisted entirely of female participants. Morphologically, tumours in the early stage were smaller, with 16 of 20 patients having a diameter of less than 2 cm, but in the late stage, 18 patients had a tumour mass of more than 5 cm.

The most common histological type in both groups was invasive ductal carcinoma. However, there were considerable disparities in the level of cell differentiation. In the early stage, the majority of tumours showed high differentiation (14/20 individuals), but in the advanced stage, 15 patients had low differentiation.

Hormonal receptor status revealed that oestrogen and progesterone hormone receptor expression was more common in early stage patients (18/20) versus just 8 patients in advanced stages. In contrast, HER2 overexpression was more common in the advanced stage group (12/20 patients).

The Ki-67 index was used to measure the rate of cell proliferation. The advanced stage group had the highest index (14/20), while the early stage group had a low proliferation index (12/20 individuals).

Lymphatic system involvement, including regional lymph node enlargement, was also more common in the late stage, with 16 and 14 patients, respectively, compared to 4 and 0 cases in the early stage. Lympho-vascular invasion and good surgical margins were also more common among the advanced patients.

The average tumour diameter in advanced stages was 6.2 cm, which was significantly larger than the early stage average of 1.5 cm. Furthermore, advanced stage patients tended to have solid, multifocal tumours (16/20 patients) with considerable proliferative activity (grade 3). Early-stage tumours, on the other hand, were typically non-solid, solitary, and localised (16/20 patients).

4. DISCUSSION

Radiological and Clinicopathological Differences Between Early and Advanced Breast Cancer Stages

This comparative study conducted at a single center offers important insights into the distinct radiological and clinicopathological characteristics that separate early-stage breast cancer from advanced-stage disease. The results reveal significant differences across various parameters, which could improve diagnostic precision and guide treatment planning.

Clinical Presentation and Symptoms

The clinical features of early versus advanced breast cancer show marked differences. Early-stage breast cancer often presents with few or no symptoms and is frequently detected through routine screening or physical exams. These tumors tend to be small, painless, and cause minimal changes in breast appearance. Conversely, advanced breast cancer is characterized by more obvious and severe symptoms, making it easier to identify clinically.

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Imaging studies such as mammography and ultrasonography in early-stage breast cancer typically show small, solid masses with features common to various tumor types. Microcalcifications and metastatic signs are rarely seen at this stage. In contrast, advanced tumors are more conspicuous on imaging, with detectable spread to lymph nodes or distant organs like the lungs and liver via CT or PET scans.

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Ultrasonography remains a vital, non-invasive tool for initial breast cancer assessment and staging. The significant imaging differences observed likely reflect tumor morphological changes as the disease advances, providing important clinical and pathological insights.

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Histopathology of early-stage breast cancer often shows ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), with tumors confined and not invading surrounding tissues. These tumors are usually small, low-grade, and show minimal vascular invasion [17].

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The cross-sectional design prevents tracking disease progression within individuals, limiting causal inferences between early and late-stage features. Important factors such as comorbidities, socioeconomic status, and screening history were not included, which could affect disease presentation.

The study also lacks advanced molecular profiling beyond basic receptor status, limiting deeper understanding of biological mechanisms. Additionally, treatment outcomes and long-term follow-up data are absent, reducing clinical applicability.

5. CONCLUSION

This study highlights clear radiological and clinicopathological differences between early and advanced breast cancer stages. At Ibnu Sina Hospital, recognizing these distinctions is essential for optimizing diagnosis and treatment strategies. The findings underscore the importance of early detection and thorough evaluation in breast cancer care. Future research with larger, multicenter cohorts, longitudinal follow-up, and comprehensive molecular analysis will further clarify breast cancer progression and may identify novel therapeutic targets.

Disclosure Statement

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- Funding Sources : None
- Ethical Approval : This study was approved by the Research Ethics Committee of the Muslim University of Indonesia with Number: 213/A.1/KEP-UMI/VI/2024
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REFERENCES

[1] for Research on Cancer IA, others. Global cancer observatory (GCO). World Heal Organ Agency Res Cancer. 2020;

[2] RI K. Data Kanker Payudara di Indonesia. Jakarta: Kementerian Kesehatan Republik Indonesia; 2023.

[3] World Health Organization. Breast Cancer Fact Sheet [Internet]. [cited 2025 Apr 27]. Available from:

https://www.who.int/news-room/fact-sheets/detail/breast-cancer

[4] MA F, F T. Breast Cancer. Baghdad; 2022.

[5] Callari M, Cappelletti V, D'Aiuto F, Musella V, Lembo A, Petel F, et al. Subtype-specific metagene-based prediction of outcome after neoadjuvant and adjuvant treatment in breast cancer. Clin Cancer Res. 2016;22(2):337–45.

[6] WA BRG. Diagnostic accuracy of mammography, clinical examination, US, and MR imaginng in preoperative assessment of breast cancer. Radiology. 2004;233:830–49.

[7] Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. Vol. 1024. Springer; 2017.

[8] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.

[9] Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24(9):2206–23.

[10] MS A, AA A, AM A, NA A, KF A, A S. Molecular subtypes of breast cancer: current role in diagnosis, prognosis and therapy. Pathophysiology. 2020;27(4):100565.

[11] Wahidin M, Djuwita R, Adisasmita A. Oral contraceptive and breast cancer risks: A case control study in six referral hospitals in Indonesia. Asian Pacific J cancer Prev APJCP. 2018;19(8):2199.

[12] Lodi M, Scheer L, Reix N, Heitz D, Carin A-J, Thiébaut N, et al. Breast cancer in elderly women and altered clinico-pathological characteristics: a systematic review. Breast Cancer Res Treat. 2017;166:657–68.

[13] Ibrahim AS, Khaled HM, Mikhail NNH, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014(1):437971.

[14] S N, M O, A M, T O. Significance of high-resolution ultrasound in the early detection of breast cancer: correlation between tumor size and prognostic factors. Ultrasound Med Biol. 2020;46(3):642–50.

[15] Y L, J C, Y Z, S Z, Y X, X W. Ultrasound features of breast cancer: association with tumor characteristics and molecular subtypes. Eur Radiol. 2023;33(1):119–25.

[16] Ji C-L, Li X-L, He Y-P, Li D-D, Gu X-G, Xu H-X. Quantitative parameters of contrast-enhanced ultrasound in breast invasive ductal carcinoma: The correlation with pathological prognostic factors. Clin Hemorheol Microcirc. 2017;66(4):333–45.

[17] Araki K, Ito Y, Fukada I, Kobayashi K, Miyagawa Y, Imamura M, et al. Predictive impact of absolute lymphocyte counts for progression-free survival in human epidermal growth factor receptor 2-positive advanced breast cancer treated with pertuzumab and trastuzumab plus eribulin or nab-paclitaxel. BMC Cancer. 2018;18:1–7.

[18] G M, R M, S F, E G, C C, I M. Prognostic factors for distant recurrence in patients with multifocal-multicentric breast cancer. Breast Cancer Res Treat. 2021;189(3):851–8.

[19] M R, S M, MA K, MH Z. Mechanobiology of tumor cell differentiation in breast cancer and its clinical implications. Cell Mol Bioeng. 2022;15(1):21–8.

[20] Y X, L L, G G, S T, Z W, M J. Comparative proteomic analysis of breast cancer revealed altered expression of key proteins related to lymph node metastasis. Proteomics Clin Appl. 2022;16(1).

[21] Turner NC, Slamon DJ, Ro J, Bondarenko I, Im S-A, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med. 2018;379(20):1926–36.

[22] Jia M, Gao X, Zhang Y, Hoffmeister M, Brenner H. Different definitions of CpG island methylator phenotype and outcomes of colorectal cancer: a systematic review. Clin Epigenetics. 2016;8:1–14.

[23] K S, US T, L L, MG G, Jakubowski J TM. Delayed and attenuated platelet inhibition response in patients with metabolic syndrome after moderate clopidogrel dose while undergoing percutaneous coronary intervention and relationship to resistin levels. Am J Cardiol. 2020;115(10):1380–6.

[24] X Z, L C, L L, X N. HER2-positive breast cancer is associated with an increased risk of positive margins after initial lumpectomy: a retrospective analysis. World J Surg Oncol. 2020;18(1):228.

[25] Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol. 2010;11(2):174–83.