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Apparent Diffusion Coefficient (ADC) Value on Magnetic Resonance Imaging (MRI) in Determining Breast Cancer and Determining Breast Cancer With Locally Advanced Expansion

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ABSTRACT

Breast cancer is the most common malignancy in women and the leading cause of cancer-related death in Indonesia. Early identification of the locally advanced stage is crucial for optimal therapy selection and prognosis. This research evaluated the diagnostic value of the Apparent Diffusion Coefficient (ADC) from diffusion-weighted MRI in detecting breast cancer and assessing locally advanced disease. Using a retrospective diagnostic test design, 50 patients who underwent breast MRI at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar, were analyzed. ADC values from DWI (b-value 800 mm²/s) were compared with histopathology for cancer confirmation and surgical reports for staging. At a cut-off of 1.088 × 10⁻³ mm²/s, ADC showed excellent performance in differentiating cancer from non-cancer (sensitivity 100%, specificity 96%, PPV 96.1%, NPV 100%, LR+ 25, LR– 0.0, accuracy 98%). However, for distinguishing locally advanced disease (cut-off 0.815 × 10⁻³ mm²/s), performance was lower (sensitivity 61.5%, specificity 75%, accuracy 68%). These findings highlight the reliability of ADC in diagnosing breast cancer but its limitations in staging, suggesting the need for integration with multimodality imaging and clinical assessment to improve accuracy and guide treatment decisions.

KEYWORDS *Apparent Diffusion Coefficient (ADC), Breast Cancer, Magnetic Resonance Imaging (MRI)*

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INTRODUCTION

Breast cancer is one of the most common malignancies found in women worldwide, with high incidence and mortality rates (Woodhams et al. 2005; Surov et al. 2019). According to the WHO in 2020, there were 2.26 million new cases, causing 684,996 deaths, and it ranked fifth as the leading cause of cancer deaths worldwide (Łukasiewicz et al., 2021). Breast cancer ranks first in the number of cancers and is one of the largest contributors to cancer deaths in Indonesia. Based on Globocan data in 2020, the number of new cases of breast cancer reached 68,858 cases (16.6%) out of a total of 396,914 new cancer cases in Indonesia, with more than 22 thousand deaths (Sung et al., 2021).

In clinical management, determining the presence of breast cancer and its advanced stage is a crucial step, considering that it impacts the selection of therapies and the prognosis of patients (Tsushima et al. 2009). As imaging technology develops, magnetic resonance imaging (MRI) with a diffusion-weighted imaging (DWI) approach has been proposed as a diagnostic support modality because it is able to capture the microscopic characteristics of tissues, especially by measuring the apparent diffusion coefficient (ADC) (Dorrius et al. 2014).

ADC value is defined as the quantification of how far water molecules are able to diffuse in tissues, predominantly influenced by cell density and cell membrane integrity (Surov et al. 2019). In practice, ADC measurements use the DWI protocol with a variety of b-values, allowing for more detailed tissue characterization, including identifying malignancies and assessing therapeutic responses (Panzeri et al. 2018). In the context of breast cancer, ADC values have been associated with tumor cell aggressiveness, where lower ADC often indicates high cellularity (Kim et al. 2019). The DWI-based MRI approach is relatively short and does

not require contrast agents, thus attracting the interest of researchers and clinicians to explore its reliability (Nilsen et al. 2010). However, research on the extent to which ADC values can determine the extent of breast cancer expansion to locally advanced stages is still controversial, especially when associated with anatomical aspects and invasion of surrounding soft tissues.

Determining advanced stages such as locally advanced is important because it directly influences therapy decisions, such as the need for neoadjuvant chemotherapy, radical mastectomy, or more aggressive radiotherapy (Virostko et al. 2017). On the other hand, delays or misdiagnosis can increase pain rates and decrease patient quality of life (Wu et al. 2015). In its development, ADC value is often touted as a promising parameter for predicting tumor invasiveness, especially in estimating cell density to assess whether the tumor has penetrated the chest wall or skin (Costantini et al. 2010). The high reliance on conventional histopathological examinations and clinical evaluations raises practical issues related to the efficiency and certainty of diagnosis. This is where the need for consistent and reproducible imaging methods becomes relevant, especially with the increasing trend of using MRI due to its superior sensitivity over mammography and ultrasound in certain cases (Dorrius et al. 2014).

There is a misalignment between the clinical need to accurately and quickly diagnose breast cancer, including determining its advanced stages, and the availability of precision non-invasive diagnostic tools (Nilsen et al. 2010). If this problem is not addressed, the risk of staging errors will continue to hinder targeted decision-making, leading to inappropriate therapy selection or delays in aggressive therapy that should be given immediately (Bufi et al. 2015). As a result, the patient's prognosis may worsen while health costs increase. Therefore, efforts to test the accuracy of ADC values in determining breast cancer in general and breast cancer with locally advanced expansion are urgent. The key question is: can ADC value bridge the gap between the desire for rapid diagnosis of precision staging and the fact that invasive diagnosis determination (histopathology and surgical reports) is still the primary reference?

Until today, most ADC value research has focused on distinguishing malignant vs. benign lesions, while the relevance of ADC values for distinguishing early-stage and locally advanced breast cancers has not been adequately reviewed (Kim et al. 2019; Wu et al. 2015). This study seeks to close this gap by highlighting two aspects at once: (1) the performance of ADC value in determining breast cancer, and (2) evaluating the ability of ADC value in recognizing cases that have achieved locally advanced expansion. A unique feature of this approach is the emphasis on surgical verification for advanced confirmation, so that it can assess the suitability of ADC data in a real context, rather than just focusing on primary pathology. Thus, this research is expected to provide added value for developing more effective MRI protocols and reduce the potential for under- or overstaging in clinical practice.

Departing from this urgency, the main objectives of this study are to: (1) assess the accuracy of ADC value in determining breast cancer, and (2) test the reliability of ADC value as an indicator of locally advanced expansion. More specifically, this study will measure sensitivity, specificity, cutoff, and other statistical indicators (PPV, NPV, LR+, LR–, and accuracy) to assess ADC value performance. The results obtained are expected to be useful for academics and medical practitioners in enriching theoretical knowledge about the pathophysiology of water molecule diffusion in tumor tissues, as well as providing real implementation guidelines in hospitals. In addition, the conclusions that emerge will help evaluate whether ADC values can be recommended as a primary biomarker or need to be combined with other methods. The analysis of this research will be closed with a discussion of the strengths, weaknesses, and practical recommendations for future researchers, as well as providing a presentation of the research methodology that details the study design and data analysis process.

RESEARCH METHODS

Research Design

This research is a diagnostic test study conducted retrospectively to determine the differences in sensitivity, specificity, PPV, NPV, LRP, and LRN of the diagnostic value of ADC values on MRI in determining breast cancer and breast cancer with locally advanced expansion. This study uses medical record data in the form of ADC values from MRI examinations and locally advanced breast cancer expansion, with the gold standard being histopathology examination and surgical reports for the removal of primary breast cancer tumors at Prof. Dr. I.G.N.G Ngoerah Hospital. The research design can be described as follows:

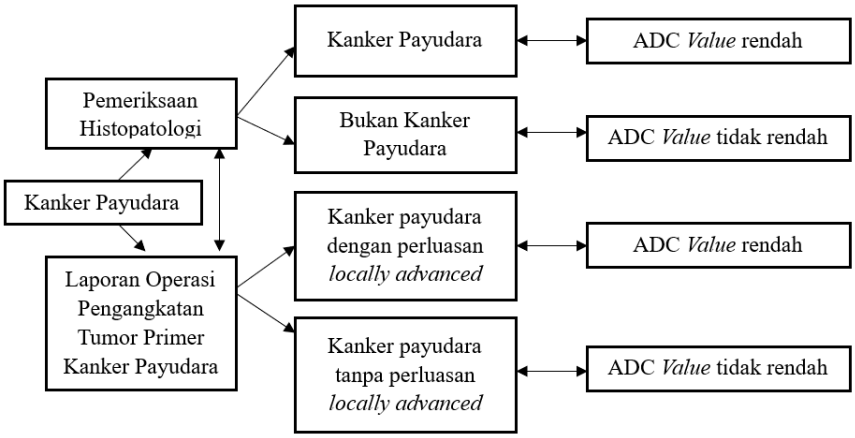

Figure 1. Research Design

Source: Original study schematic developed by research team based on STARD guidelines for diagnostic test reporting

Research Location and Time

The research was carried out at the Medical Record Installation and Radiology Installation at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar, Indonesia, from January 2020 until January 2025.

Population and Sample

The accessible population consists of breast cancer patients who have undergone MRI examinations at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar, Indonesia, starting in January 2020 until the required number of patients was reached. The sample for this study is a subset of the accessible population that meets the inclusion and exclusion criteria, resulting in eligible subjects.

Sampling Techniques

The research sample was obtained using a nonrandom sampling method, specifically consecutive sampling, from the medical records of breast cancer patients who underwent MRI and had histopathological confirmation and surgery reports at Prof. Dr. I.G.N.G Ngoerah Hospital, starting in January 2020 until the sample size was fulfilled.

Data collection techniques include primary data (ADC scores, histopathology reports, and surgery) and secondary data (patients' medical records such as age, gender, and stage of cancer). Data analysis was conducted descriptively for demographic characteristics and ADC value statistics, followed by diagnostic analysis using *Receiver Operating Characteristic* (ROC) to determine the *cut-off of* ADC values, as well as calculating sensitivity, specificity, *positive predictive value* (PPV), *negative predictive value* (NPV), and accuracy.

Inferential statistical analysis was performed using the *Chi-square test* and logistic regression with a significance level of $p < 0.05$. This research has received ethical approval, with patient identity confidentiality maintained. Key limitations include potential *selection bias* due to the retrospective design and limited sample sizes in the *locally advanced* subgroups. The results of the study are expected to provide clinical guidance on the use of ADC values in the diagnosis and staging of breast cancer.

RESULTS AND DISCUSSION

Characteristics of Research Samples

This study involved as many as 50 patients with breast cancer. The characteristics of the patients are presented in **Table 1.**

Table 1. Characteristics of Breast Cancer Patients

Characteristic		Result
Age (years)		
≤ 40	n (%)	14 (28)
41-50	n (%)	18 (36)
51-60	n (%)	12 (24)
≥ 61	n (%)	6 (12)
Gender		
Man	n (%)	0 (0)
Woman	n (%)	50 (100)

Source: Compiled from hospital electronic medical records (EMR) system, including age and gender distributions

The majority of patients were in the age range of 41-50 years (36%), followed by ≤ age 40 years (28%), 51-60 years (24%), and ≥ 61 years (12%). All patients in this study were women (100%). These demographic characteristics provide an overview of the age groups that are more prone to breast cancer in the study population, with the predominance of patients in the age range of 41-50 years

Overview of ADC Value Characteristics, Histology, and Operation Report

Descriptive Statistics ADC Value

In this study, the Apparent Diffusion Coefficient (ADC) value on MRI was analyzed to distinguish between breast and non-breast cancer, as well as to distinguish breast cancer with locally advanced expansion.

Table 2. Descriptive ADC Value Statistics of Breast Cancer Patients

	n	Minimum	Maximum	Mean	Std. Deviation
ADC Value In Determining Breast Cancer	50	0.368	2.730	1.139	0.471
ADC Value in Determining Breast Cancer with Locally Advanced Expansion	24	0.368	0.963	0.756	0.152

Source: Quantitative analysis of MRI DWI sequences (b=800 mm²/s) using Siemens Syngo.via workstation

Table 2. shows the average ADC value for patients with breast cancer which is $1.139\ x\ 10^{-3} mm^2/s$ (SD = 0.471), with a minimum value of 0.368 $x\ 10^{-3} mm^2/s$ and a

maximum of 2.730 $x\ 10^{-3}mm^2/s$. Meanwhile, the ADC value for patients with locally advanced breast cancer had a lower average, which was 0.756 $x\ 10^{-3}mm^2/s$ (SD = 0.153) with a minimum value of 0.368 $x\ 10^{-3}mm^2/s$ and a maximum of 0.963 $x\ 10^{-3}mm^2/s$.
These results show a difference in ADC values between the general breast cancer group and the locally advanced expansion group. Lower average ADC value in *the locally advanced* expansion group indicated that tumors with more limited diffusion of water molecules were more likely to develop aggressively.

Distribution of Histopathology Results and Surgery Reports

Table 3. Distribution of Confirmation of Histopathological Results of Breast Cancer Patients

		Result
Not Breast Cancer	n (%)	25 (50)
Breast Cancer	n (%)	25 (50)
Total		50 (100)

Source: Cross-referenced pathology reports from hospital Department of Anatomical Pathology

Table 4. Distribution of Confirmation of Results of Breast Cancer Patient Surgery Reports

		Result
Breast Cancer Without Locally Advanced Expansion	n (%)	12 (48)
Breast Cancer With Locally Advanced Expansion	n (%)	13 (52)
Total		25 (100)

Source: Operative notes reviewed from hospital Surgery Department archives

Table 3. showing the histopathological distribution shows that out of 50 patients, 25 patients (50%) were diagnosed as non-breast cancer and 25 patients (50%) as breast cancer. Based on the surgery report in **Table 4**, of the 25 patients with breast cancer, 13 patients (52%) experienced locally advanced expansion, while 12 patients (48%) did not experience the expansion. These results showed that about half of histopathologically confirmed breast cancer cases also had more advanced stages confirmed on the surgery report.

Receiver Operating Characteristic (ROC) Analysis and ADC Value Cut-off Point Determination

Receiver Operating Characteristic (ROC) analysis with Area Under the Curve (AUC) was used to evaluate the ability of ADC values to differentiate patients with and without breast cancer, as well as to differentiate breast cancer with and without locally advanced expansion.

ROC To Determine Breast Cancer

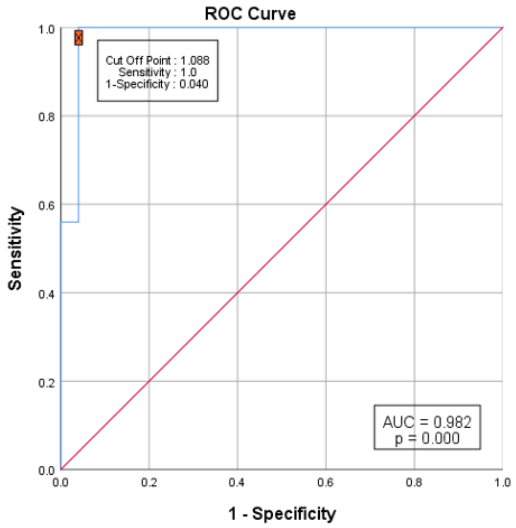

Figure 2. ROC ADC Value Curve in Determining Breast Cancer with Area Under the Curve (AUC) of 0.982 (95% CI: 0.947 – 1,000, p < 0.001)
Source: ROC analysis performed using MedCalc v20.115 software with DeLong method for CI calculation

Based on ROC analysis, the optimal cut-off point of the ADC value to determine breast cancer was $1.088\ x\ 10^{-3} mm^2/s$, with an Area Under the Curve (AUC) of 0.982 (95% CI: 0.947 – 1,000, p < 0.001). The highest Youden's Index value (0.960) indicates that this model has an optimal balance between sensitivity and specificity. Sensitivity 100% (all cases of breast cancer detected), specificity: 96% (96% of negative cases correctly identified). A very high AUC value (0.982) indicates that the ADC value is an excellent predictor in distinguishing breast cancer from non-breast cancer.

ROC To Determine Breast Cancer with Locally Advanced Expansion

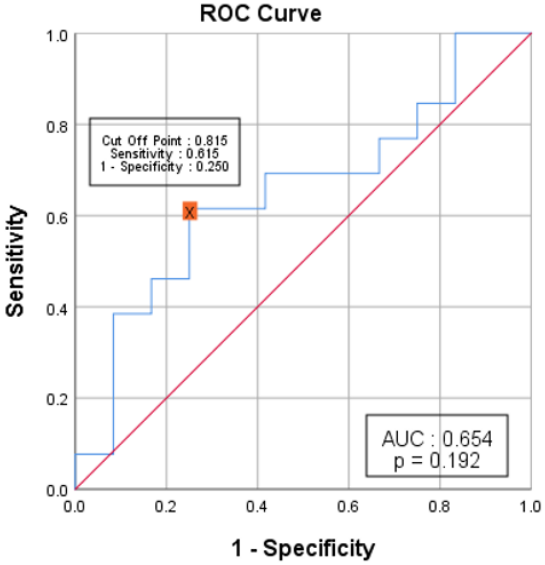

Figure 3. ROC ADC Value Curve in Determining Locally Advanced Breast Cancer with AUC of 0.654 (95% CI: 0.433 – 0.874, p = 0.192)
Source: ROC analysis performed using MedCalc v20.115 software with DeLong method for CI calculation

In the group of breast cancer with locally advanced expansion, the optimal cut-off point obtained was 0.815 $x\ 10^{-3}mm^2/s$, with an AUC of 0.654 (95% CI: 0. 433 – 0. 874, p = 0.192). The sensitivity is 61.5%, the specificity is 75%. The highest Youden's Index on the ROC curve above is 0.365 at a cut-off point of 0.815 $x\ 10^{-3}mm^2/s$. Although the value is not high, it is this cut-off point that provides the best balance between sensitivity and specificity in the available data.

These results show that although the ADC Value is able to achieve an AUC of 0.654, statistically (p = 0.192) the value is not significant and not strong enough to accurately distinguish locally advanced breast cancer. When sensitivity and specificity are still in the range of 60% – 75%, ADC Value is less effective if used as a single determinant. AUC values that do not reach 0.7 and p-values above 0.05 indicate that ADC Values do not have satisfactory predictive power in separating locally advanced and locally advanced breast cancer.

Diagnostic Value of ADC Value in Determining Breast Cancer

Table 5. ADC Value Diagnostic Value in Determining Breast Cancer Based on Histopathology

ADC value	Histopathology		Sn	Sp	PPV	NPV	LR+	LR-	Accuracy
	Breast Cancer n (%)	Not Breast Cancer n (%)							
< 1.088	25 (100)	1 (4)							
≥ 1.088	0 (0.0)	24 (96)	100%	96%	96.1%	100%	25	0	98%
Total	25 (100)	25 (100)							

Source: Calculated from 2×2 contingency tables using standard diagnostic test formulas

Diagnostic analysis of ADC values to determine breast cancer is shown in **Table 5.** With a cut-off ADC value of 1.088 $x\ 10^{-3}mm^2/s$, sensitivity reached 100%, indicating that this ADC value successfully identified all breast cancer cases in this study. The specificity was also high (96%), indicating that most patients without breast cancer were correctly identified. PPV value 96.1% indicates that of all patients who were detected positive, 96.1% actually had breast cancer. Meanwhile, an NPV value of 100% means that all patients classified as negative really do not have breast cancer.

From the LR+ value of 25. and LR- of 0, the ADC value shows excellent diagnostic characteristics. With an accuracy of 98%, these results show that ADC value is a reliable biomarker in determining breast cancer.

ADC Value Diagnostic Value in Determining Breast Cancer with Advanced Locally Expansion

Table 6. ADC Value Diagnostic Value in Determining Breast Cancer With Advanced Locally Expansion Based on Surgery Report

ADC value	Operations Report		Sn	Sp	PPV	NPV	LR+	LR-	Accuracy
	Breast Cancer With Expansion n (%)	Breast Cancer Without Expansion n (%)							
< 0.815	5 (38.5)	9 (75)	61,5%	75%	72,7%	64,3%	2,46	0,51	68%

≥ 0.815	8 (61.5)	3 (25)
Total	13 (100)	12 (100)

Source: Calculated from 2×2 contingency tables using standard diagnostic test formulas

Table 6. shows that for the *cut off* ADC value of 0.815 $x\ 10^{-3}mm^2/s$, the sensitivity obtained is quite 61.5%, but the specificity is moderately 75%. Although not as high as 90% – 100%, this sensitivity-specificity combination is relatively more balanced than if we only prioritize high sensitivity but allow very low fall specificity. PPV value of 72.7% indicates that around 27.3% of subjects who were detected positive did not have locally advanced expansion, while an NPV of 64.3% showed that there were still 35.7% of subjects classified as negative when in fact they were expanded. The LR+ values of 2.46 and LR- of 0.51 also indicate that the ADC Value provides little diagnostic information, but is not yet strong as the determinant.

Overall, the 68% accuracy shows that about 32% of classifications using this cut off are still inaccurate. Thus, ADC Value is not reliable enough in determining breast cancer with locally advanced expansion when standing alone.

Diagnostic Value of ADC Value in Determining Breast Cancer

This study aims to evaluate the ability of ADC value as a diagnostic marker in determining breast cancer patients and not breast cancer. Theoretically, the use of ADC values is based on the principle that the diffusion of water molecules in tissues is inhibited in areas with high cell density, such as in malignancies (Woodhams et al. 2005; Surov et al. 2019). The initial hypothesis proposed is that ADC values have excellent diagnostic value in distinguishing malignant and benign lesions in the breast. The statistical objectives to be achieved include the calculation of sensitivity, specificity, *positive predictive value* (PPV), *negative predictive value* (NPV), positive and negative *likelihood ratio* (LR), and overall accuracy. Through the *Receiver Operating Characteristic* (ROC) approach and *Area Under the Curve* (AUC) calculation, this study tried to confirm whether the ADC value is reliable enough as a biomarker for early detection of breast cancer. In the context of this study, the ADC value was measured by the DWI technique on breast MRI, using a b value of 800 s/mm² to obtain an optimal diffusion profile (Dorrius et al. 2014; Tsushima et al. 2009).

The statistical method used included ROC analysis to determine the ADC *cut-off* value, followed by the calculation of sensitivity and specificity at the optimal cut-off point. ROC analysis was chosen because it was able to provide a comprehensive picture of the diagnostic performance of a method. AUC approaching 1 indicates excellent performance, while AUC approaching 0.5 indicates performance equivalent to random guessing (Baltzer et al. 2010). The study also included Youden's Index to find the optimal balance between sensitivity and specificity. Furthermore, calculating PPV, NPV, LR+, and LR- provides detailed information about the accuracy of ADC values in identifying which samples are breast cancer positive, and in accurately ruling out non-breast cancer cases (Deeks and Altman 2004). It is hoped that this series of statistical tests can provide a strong foundation to assess how much ADC value can improve the accuracy of diagnosis.

The results showed that the optimal *cut-off* value of ADC was 1.088 $x\ 10^{-3}mm^2/s$ to separate breast cancer and non-breast cancer. This value was obtained from the analysis of ROC with AUC reaching 0.982 (95% CI: 0.947 – 1,000), $p < 0.001$. These findings suggest that ADC values approach excellent diagnostic performance where the higher the AUC, the stronger the ability to distinguish between negative and positive conditions (Surov et al. 2019; Tsushima et al. 2009). At the cut-off point, sensitivity was recorded at 100%, indicating that the entire breast cancer patient was detectable, and the specificity was 96%, indicating that

96% of patients who did not actually have breast cancer were successfully removed from the cancer suspect.

From the results above, Youden's Index reaches 0.960 which means that the classification model with ADC values has an optimal balance between sensitivity and specificity. In addition, a PPV of 96.1% indicates that of all patients who tested positive by ADC value, about 96.1% actually had breast cancer. A 100% NPV value reinforces the conclusion that if the ADC value is above the *cut-off* of 1.088 $x\ 10^{-3}mm^2/s$, then it is more likely that the patient is not cancerous (Woodhams et al. 2005). A positive likelihood ratio (LR+) reaches 25 and a negative likelihood ratio (LR-) equal to 0 confirms that a positive test result significantly increases the likelihood of cancer, while a negative result reduces the likelihood of cancer to close to zero (Deeks and Altman 2004). Overall, the accuracy of the test reached 98%, indicating that the ADC value has the potential to be a strong confirmation modality for the early diagnosis of breast cancer.

The AUC value of 0.982 is statistically very high ($p < 0.001$), indicating that the ADC value is able to consistently distinguish subjects with cancer versus non-cancer (Matsubayashi et al. 2013). Its clinical significance lies in how ADC value can trim false negatives as well as false positives. Successfully identifying all breast cancer patients (100% sensitivity) is critical to prevent misdiagnosis that can be fatal. The 96% specificity is also quite promising in reducing unnecessary biopsies in patients who do not actually have cancer (Tamura et al. 2012). This result is in line with the research hypothesis, namely that the ADC value has an excellent diagnostic value in determining breast cancer.

These findings are consistent with previous studies, where the *cut-off* ADC value for distinguishing breast cancer from non-cancerous lesions are often in the range of 0.9 – 1.3 $x\ 10^{-3}mm^2/s$, depending on the DWI protocol (Tsushima et al. 2009; Surov et al. 2019). A meta-analysis by Dorrius et al. (2014) noted the sensitivity and specificity of ADC value in the range of 80–90%. These results also confirm the results of high sensitivity and specificity in this study. These results are likely to be achieved with a more controlled MRI protocol standard, precise and uniform b-value ranges, and careful ROI determination methods (Baltzer et al. 2010). However, some literature mentions the potential for overlap in ADC values, especially in certain types of breast cancer such as mucinous carcinoma which have relatively higher ADC value (Woodhams et al. 2005). This confirms the importance of confirming ADC findings with clinical data or additional imaging such as *Dynamic Contrast-Enhanced* MRI.

Theoretically, the results of this study reinforce the biological basis that breast cancer is characterized by relatively high cell density, inhibiting the random movement of water molecules in extracellular space (Ikeda et al. 2010). Lower ADC value reflect water diffusion restrictions, in line with the concept that invasive tumor tissues contain more cells, cell membranes, and intracellular proteins. These results add to the validation of the use of ADC value as one of the key parameters in assessing the level of malignancy in the breast (Tsushima et al. 2009).

From a clinical point of view, this information can confirm that ADC values can be integrated as part of routine breast MRI protocols, particularly in certain cases where mammography and ultrasound give dubious results. The addition of DWI to the MRI protocol is quite brief without the need for a contrast agent, thus lowering costs and shortening the duration of the examination (Bogner et al. 2009). When the ADC value is below *the cut-off* of 1.088 $x\ 10^{-3}mm^2/s$, the patient is more likely to have breast cancer, so a biopsy can be performed immediately. In contrast, for ADC values above the *cut off*, the likelihood of cancer is much lower and radiological *follow-up* can be considered first (Surov et al. 2019).

Overall, the results of this study show that the ADC value has a good diagnostic performance in determining breast cancer. A *cut-off value* of 1,088 $x\ 10^{-3}mm^2/s$ with an AUC of 0.982 has been shown to be able to combine 100% sensitivity and 96% specificity,

making it a good instrument for sorting out patients who are most likely to have malignant lesions. These findings are consistent with the hypothesis that ADC values have good diagnostic value in determining breast cancer. However, more extensive and standardized research is needed to maintain the validity of results across populations and histopathological subtypes. By implementing ADC value as part of the breast MRI protocol, it is hoped that the efficiency and accuracy of breast cancer diagnosis can continue to improve.

ADC Value Diagnostic Value in Determining Breast Cancer with Locally Advanced Expansion

This study also aims to evaluate the ability of ADC values in determining breast cancer with and without *locally advanced expansion*. In a clinical context, the determination of advanced stages is important because it influences the selection of therapies, including the need for radical mastectomy, more aggressive radiotherapy, or even systemic therapy approaches (Wu et al. 2015). The research hypothesis states that the ADC value, which reflects the restriction of water molecule diffusion due to cell density, may exhibit strong performance in separating the breast cancer group without *locally advanced* expansion from the group that has experienced *locally advanced expansion*. Its application is expected to be able to provide a framework for early detection of tumor aggressiveness in order to develop more appropriate therapy strategies. Thus, this study specifically highlights the correlation between *ADC value* cut-off and *locally advanced* expansion rates of breast cancer.

Based on ROC analysis, the optimal cut-off point of ADC value to predict *locally advanced* expansion was $0.815\ x\ 10^{-3} mm^2/s$, with an AUC of 0.654 (95% CI: 0.433 – 0.874, p = 0.192). The sensitivity is 61.5% and the specificity is 75%. The PPV value is also relatively moderate in the range of 72.7%, while the NPV reaches 64.3%. This finding is accompanied by Youden's Index of 0.365, which shows a relative balance between sensitivity and specificity at *the cut off*. In general, AUC below 0.7 indicates that the model's performance is still limited in distinguishing breast cancer with or without locally advanced expansion (Nilsen et al. 2010). Although the sensitivity and specificity were relatively balanced, the statistical insignificance (p = 0.192) and wide confidence intervals illustrated that the ADC Value did not have satisfactory predictive power in distinguishing breast cancer with or without *locally advanced expansion.*

Theoretically, we would expect a lower ADC value to indicate that tumor cells are denser and expand aggressively (Costantini et al. 2010). However, anatomical components such as skin, muscle, and lymph node involvement also influence the determination of advanced stages, which do not appear to be well reflected by ADC values alone (Kim et al. 2019). When compared to the initial hypothesis that ADC values can well detect the rate of *locally advanced* expansion, the results obtained are less supportive.

When compared to the initial hypothesis that ADC Value would be able to detect better, these results are not supportive. ADC Value is still susceptible to *false positives* and *false negatives* at a level that cannot be ignored (Wu et al. 2015). This means that ADC values are less effective in filtering cases that have actually reached the *locally advanced* stage. Some literature reports mixed results, with some studies showing a strong correlation of ADC values to cancer aggressiveness levels (Kim et al. 2019; Panzeri et al. 2018). However, differences in MRI protocols, b-values, and histopathological heterogeneity may explain why these findings are inconsistent.

In practical implications, a sensitivity of 61.5% suggests that out of every 100 patients with *locally advanced* breast cancer, only about 62 are correctly detected, so there is still a risk of under-diagnosis for nearly 38 patients (Guyatt et al., 2011). On the other hand, 75% specificity means that out of every 100 individuals without *locally advanced expansion*, 75 people will be correctly identified negative, while another 25 could potentially be falsely

categorized as positive. The clinical implication is that there are still a portion of patients who are not detected (*false negative*) and healthy groups who may receive overaction (*false positive*), thus affecting the efficiency of management.

In the context of breast cancer, under-diagnosis can delay therapy that should be given immediately, while over-diagnosis risks triggering unnecessary invasive interventions (Nilsen et al., 2010). Although this sensitivity and specificity is moderate, the use of imaging methods or other supporting markers may be considered to improve diagnostic accuracy. Thus, this test can still be useful in initial screening, but the results need to be accompanied by a comprehensive evaluation to make more precise clinical decisions (Kim et al., 2019).

This research has several limitations that must be acknowledged. First, the relatively small size of the subpopulation with locally advanced breast cancer (13 patients out of a total of 25 cancer cases) may affect the stability of AUC estimates (Virostko et al. 2017). Second, a major limitation occur in the use of a subset of "*post-hoc*" data. The researchers focused on 25 breast cancer-positive samples out of a total of 50 research samples and then divided them again into 13 breast cancer-positive samples with *locally advanced* expansion, the other 12 without *locally advanced expansion*. This kind of separation method is prone to causing *working data analysis bias*, which is a bias that arises from the data sorting process that is not planned from the beginning (Rothman et al. 2008).

This bias can occur due to sample size reduction, which lowers *statistical power* and makes it difficult to detect the effects that actually exist. It can also be caused by the selection of a subset of data that is not neutral, where the analysis is focused only on a specific group (only positive samples), rather than the entire data. As a result, low AUC may not simply be a reflection of the inadequacy of the ADC value, but also reflects a characteristic imbalance between subgroups. This weakens internal validity, resulting in a decrease in significance (Guyatt et al. 2011).

In order to reduce *this biased working data analysis*, it is recommended in the future to: (1) Formulate a subgroup analysis plan from the beginning, including the minimum target of subjects with *a locally advanced* stage. (2) Increase the number of participants in prospective design or collaboration between medical facility centers to avoid subgroups that are small (Virostko et al. 2017). (3) Consider corrective analysis methods such as bootstrapping when samples are limited. (4) Combine ADC with other parameters, e.g. volume calculation, chest wall infiltration assessment, and lymphodyd status on T2 and *Dynamic Contrast-Enhanced* MRI, to improve accuracy. All of these steps will reduce the potential for *biased working data analysis* and improve ADC value utility.

Overall, the results show that the ADC value is not optimal as a single parameter to distinguish breast cancer from *locally advanced* expansion. This can be seen from the low AUC (0.654), insignificant p-value, and moderate sensitivity-specificity, and *not too high* predictive values. This phenomenon confirms that the anatomical involvement that characterizes *locally advanced expansion* is difficult to capture by assessing diffusion within the tumor alone. These findings are in line with the literature suggesting the need for a multimodal approach including *Dynamic Contrast-Enhanced* MRI imaging, T2-weighted *imaging*, and clinical assessment to appropriately assess *locally advanced* expansion staging . Although ADC value have been shown to be useful in several domains of diagnosis and evaluation of therapeutic responses, this study highlights that ADC value, particularly for *locally advanced* setting, cannot stand alone as clinical decision-makers. Follow-up studies with larger populations, integrated MRI protocols, and histopathological subtype analysis are needed to clarify the role of ADC value in determining breast cancer with *locally advanced expansion*.

CONCLUSION

Based on the results and discussions presented in this study, the following conclusions can be drawn: ADC *value* has good diagnostic value in determining breast cancer, with a sensitivity of 100%, specificity of 96%, PPV of 96.1%, NPV of 100%, LR+ of 25, LR– of 0.0, accuracy of 98%, and an AUC of 0.982 at *the cut-off* 1.088. These results suggest that the ADC value is a reliable parameter to distinguish patients with or without breast cancer in general. The ADC *value* had a diagnostic value that was not optimal in determining breast cancer with *locally advanced* expansion at *a cut-off* of 0.815, with a sensitivity of 61.5%, specificity of 75%, PPV of 72.7%, NPV of 64.3%, LR+ of 2.46, LR– of 0.51, accuracy of 68%, and an AUC of 0.654 (p = 0.192). The low AUC and insignificant p-value indicate that ADC values are not optimal in separating the breast cancer group with or without *locally advanced expansion.*

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