

Association of intratumoral and peritumoral apparent diffusion coefficients with stromal tumor-infiltrating lymphocyte levels in primary triple-negative breast cancer: a retrospective 3-T MRI study

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Abstract

Background

Tumor-infiltrating lymphocytes (TILs) are associated with treatment response and prognosis in triple-negative breast cancer (TNBC), but their assessment requires tissue sampling. We investigated whether routine pretreatment imaging findings, particularly intratumoral and peritumoral apparent diffusion coefficient (ADC) measurements on 3-T breast MRI, were associated with stromal TIL levels and evaluated an exploratory MRI-based model.

Methods

This single-center retrospective study included 79 consecutive women with primary TNBC assessed between November 2016 and October 2023. High TIL status was defined as stromal TILs $\geq 10\%$ in pretreatment biopsy specimens. Mammographic, ultrasonographic, MRI, and ^{18}F -fluorodeoxyglucose PET/CT findings were analyzed when available. A prespecified MRI-based logistic regression model included intratumoral ADC, peritumoral ADC, and MRI margin. Discrimination was assessed by receiver operating characteristic analysis and internally validated using 1,000 bootstrap resamples. Associations with pathological complete response (pCR) were explored.

Results

High TIL status was present in 57 of 79 participants (72.2%). Among 76 participants with MRI, higher intratumoral ADC (adjusted odds ratio [OR], 6.96; 95% confidence interval [CI], 2.47–19.67; $p < 0.001$) and lower peritumoral ADC (adjusted OR, 0.27; 95% CI, 0.11–0.66; $p = 0.004$) were independently associated with high TIL status. The exploratory MRI-based model had an apparent area under the curve (AUC) of 0.934 (95% CI, 0.879–0.989) and an optimism-corrected AUC of 0.914. Intratumoral ADC alone had an AUC of 0.856 (95% CI, 0.768–0.944). The associations remained consistent after adjustment for the MRI system and in the analysis restricted to the predominant Ingenia 3.0T system. In exploratory analyses, pCR was more frequent in participants with high versus low TIL status (58.1% vs. 7.7%; $p = 0.001$) and in those with high versus low intratumoral ADC (57.1% vs. 8.3%; $p = 0.003$).

Conclusions

Routine intratumoral and peritumoral ADC measurements were associated with high stromal TIL status in this single-center TNBC cohort. The exploratory MRI-based model showed good discrimination after bootstrap correction. External multicenter evaluation is required before clinical use.

Background

Breast cancer is the most commonly diagnosed malignancy among women, with an estimated 2.3 million new cases occurring globally each year [1]. Among its subtypes, triple-negative breast cancer (TNBC) accounts for 10–20% of cases and is defined by the lack of estrogen receptor (ER) and progesterone receptor (PgR) expression and the absence of human epidermal growth factor receptor 2 (HER2) amplification [2]. Unlike other subtypes, TNBC does not respond to endocrine or HER2-targeted therapies, resulting in limited treatment options and a generally poor prognosis. Although chemotherapy remains the cornerstone of TNBC treatment, the recent development of immune checkpoint inhibitors has renewed interest in identifying reliable immunological biomarkers.

Tumor-infiltrating lymphocytes (TILs), as a key component of the tumor immune microenvironment, have been recognized as both prognostic and predictive biomarkers in breast cancer. TILs are particularly prominent in highly proliferative tumors such as TNBC and HER2-positive breast cancer [3]. Higher stromal TIL levels have also been associated with improved response to immune checkpoint inhibitor–based therapy in TNBC, suggesting a potential role as a treatment-response biomarker [4, 5].

High TIL levels have been associated with improved therapeutic response, higher pathological complete response (pCR) rates, and better prognosis in both TNBC and HER2-positive breast cancer [2, 6, 7]. However, accurately evaluating TILs remains challenging due to the complexity of the tumor microenvironment, which includes diverse populations of immune and stromal cells [8, 9]. Therefore, there is a need for more reliable and clinically practical methods to assess TILs.

Currently, the gold standard for TIL evaluation depends on histopathological analysis of biopsy or surgical specimens. However, this approach is inherently invasive and limited by tumor heterogeneity and sampling error. Noninvasive imaging techniques may offer a more comprehensive assessment of the tumor microenvironment. Among these, diffusion-weighted magnetic resonance imaging (DWI) enables calculation of the apparent diffusion coefficient (ADC), which reflects tissue cellularity and may correlate with immune-related features such as TIL infiltration. Compared with more complex approaches such as radiomics or deep learning, ADC provides a simple, quantitative, and reproducible parameter that is widely available in clinical practice.

Previous imaging studies have explored associations between TIL levels and various parameters, including an ultrasonography-based TIL score [10] and MRI-based radiomics models [11–13]. Standardized recommendations for TIL assessment have also been extended to residual disease after neoadjuvant therapy and carcinoma in situ [14]. More recently, Gigli et al. reported that conventional MRI features, particularly ADC values and enhancement characteristics, were associated with TIL levels in breast cancer [15]; however, their study analyzed a mixed-subtype cohort with relatively few TNBC cases. Many of these methods remain experimental, lack external validation, or require multimodal integration that is not routinely feasible. Moreover, subtype-specific evidence in TNBC remains limited despite the strong clinical relevance of TILs in this subtype. Furthermore, in daily clinical practice, not all participants undergo the same preoperative imaging examinations, making the clinical utility of a multimodality approach uncertain.

Therefore, this retrospective study aimed to assess whether routinely acquired intratumoral and peritumoral ADC measurements on pretreatment 3-T breast MRI were associated with high stromal TIL levels in primary TNBC and to evaluate the discrimination and internal validity of an exploratory MRI-based model. We also examined associations between other imaging findings from mammography, ultrasonography, and PET/CT and TIL status. Finally, we explored associations of TIL status and intratumoral ADC with pCR.

Methods

Participants and Data Collection

This single-center retrospective study was approved by the institutional review board (approval number: 5069). Study details were disclosed on the institutional bulletin board, allowing participants the opportunity to opt out.

Eligible participants were women with primary TNBC. Participants were consecutively identified from the institutional breast cancer registry. Among 1,192 patients with breast cancer assessed between November 2016 and October 2023, 94 had primary TNBC. Fifteen were excluded because pretreatment biopsy specimens were unavailable, leaving 79 participants for the final analysis (Fig. 1). All included participants had pretreatment biopsy specimens adequate for TIL assessment and underwent both mammography and ultrasonography. Contrast-enhanced MRI and ^{18}F -FDG PET/CT were not mandatory and were analyzed when available. Of the 79 participants, 76 underwent pretreatment MRI and 63 underwent ^{18}F -FDG PET/CT. TNBC diagnosis was confirmed by immunohistochemical (IHC) analysis of ER, PgR, and HER2 expression. ER and PgR statuses were assessed by IHC, with positivity defined as nuclear staining in $\geq 1\%$ of tumor cells in accordance with American Society of Clinical Oncology and the College of American Pathologists guidelines. HER2 status was determined by IHC and further evaluated using fluorescence in situ hybridization in cases with equivocal IHC (2+) results. Tumors negative for both hormone receptors and HER2 were classified as TNBC. The Ki-67 labeling index was measured using IHC with the MIB-1 antibody, and the percentage of positively stained tumor nuclei was recorded. Histological grade and lymphatic and venous invasion status were obtained from routine pathological reports based on pretreatment biopsy specimens collected before systemic therapy. Histological grade was recorded according to the Nottingham histological grading system. Lymphovascular invasion was considered present when either lymphatic or venous invasion was recorded. Germline *BRCA1/2* mutation status was assessed via next-generation sequencing of peripheral blood samples, performed at a certified clinical genetics laboratory when clinically indicated or with participant consent.

TIL Evaluation

TIL levels were assessed using hematoxylin and eosin-stained slides prepared from pretreatment biopsy specimens. The evaluation followed the criteria established by the International Immuno-Oncology

Biomarker Working Group (2017), which quantifies TILs as the percentage of tumor stroma occupied by lymphocytes. For this study, a threshold of $\geq 10\%$ defined the high-TIL group, while cases with $< 10\%$ TILs were classified as the low-TIL group [7, 9, 14]. All TIL assessments were performed by a board-certified surgical pathologist with extensive experience in breast pathology, following standardized criteria established by the International Immuno-Oncology Biomarker Working Group.

Pathological Complete Response Assessment

Among participants who received neoadjuvant systemic therapy and had available surgical pathology, pathological complete response (pCR) was evaluated as an exploratory clinical outcome. pCR was defined as the absence of residual invasive carcinoma in the breast and axillary lymph nodes (ypT0/is ypN0) [16].

Imaging Protocols

Mammography Protocol

Mammographic images were acquired in craniocaudal and mediolateral oblique projections using a Senographe Essential system (GE Healthcare, Milwaukee, WI, USA). Spot compression and magnification views were obtained when necessary.

Ultrasonography Protocol

Bilateral whole-breast ultrasonography was performed using high-frequency (8–10 MHz) probes (Hl VISION Ascendus; Hitachi-Aloka Medical, Mitaka, Tokyo, Japan). Lesions were assessed in at least two orthogonal planes: transverse and longitudinal.

MRI Protocol

Participants who underwent breast MRI were examined in the prone position using one of two 3.0-T systems: a Vantage Titan system (Toshiba Medical Systems, Ohtawara, Japan) with a 16-channel phased-array breast coil or an Ingenia 3.0T system (Philips Healthcare, Best, the Netherlands) with a SENSE Breast 7M coil. MRI examinations were performed as part of routine pretreatment evaluation, and menstrual cycle timing was not systematically controlled.

For the Vantage Titan system, T2-weighted imaging (T2WI) was performed with a repetition time/echo time (TR/TE) of 4,600/60 ms, a field of view (FOV) of 250×350 mm, a slice thickness/gap of 3.0/0.6 mm, a matrix size of 256×512 , and a flip angle of 90° . Dynamic contrast-enhanced T1-weighted imaging (DCE-T1WI) was performed with a TR/TE of 5.5/2.5 ms, an FOV of 250×350 mm, a slice thickness of 1.0 mm, a matrix size of 242×304 , and a flip angle of 15° . Diffusion-weighted imaging (DWI) was

performed with a TR/TE of 10,045/84 ms, an FOV of 250 × 320 mm, a slice thickness of 3.0 mm, a matrix size of 104 × 103, and a flip angle of 90°, using b values of 0, 1000, and 2000 s/mm².

For the Ingenia 3.0T system, T2WI was performed with a TR/TE of 5,585/58 ms, an FOV of 250 × 320 mm, a slice thickness/gap of 3.0/0.6 mm, a matrix size of 336 × 316, and a flip angle of 90°. DCE-T1WI was performed with a TR/TE of 3.4/1.66 ms, an FOV of 250 × 320 mm, a slice thickness of 2.0 mm, a matrix size of 323 × 311, and a flip angle of 15°. DWI was performed with a TR/TE of 10,045/84 ms, an FOV of 250 × 320 mm, a slice thickness of 3.0 mm, a matrix size of 104 × 134, and a flip angle of 90°, using b values of 0, 1000, and 2000 s/mm².

Contrast-enhanced imaging was performed after a bolus injection of gadoteridol (Bracco-Eisai) or gadoterate meglumine (Guerbet) at 0.2 mL/kg body weight, followed by a 20-mL saline flush. For both systems, ADC maps were automatically generated on the respective MRI systems using vendor-provided software with monoexponential fitting of signal intensities acquired at all three b values (0, 1000, and 2000 s/mm²). The system software versions were SM = V2.50*R007 for the Vantage Titan and 5.6.1 for the Ingenia 3.0T. The ADC maps were subsequently exported to an institutional image-viewing workstation for ROI placement and ADC measurements.

¹⁸F-FDG PET/CT Protocol

Preoperative ¹⁸F-FDG PET/CT was performed when deemed necessary by the attending physician. Images were acquired using dedicated ¹⁸F-FDG PET/CT scanners (Biograph Sensation 16, Biograph mCT-s (64) 4R, Biograph Vision 600; Siemens, Erlangen, Germany). Image reconstruction was performed using an ordered-subset expectation-maximization algorithm, with four iterations and five subsets for the Biograph Vision 600, and two iterations and 21 subsets for the Biograph mCT 64. Gaussian filters were applied for post-processing (4.0-mm filter for the Biograph Vision 600; 6.0-mm filter for the Biograph mCT 64). After confirming that blood glucose levels were < 200 mg/dL, participants were injected with 3.9 ± 0.2 MBq/kg of ¹⁸F-FDG, with a mean injection activity of 219.5 ± 46.5 MBq and a scan time of 78.3 ± 9.6 min post-injection. The maximum standardized uptake value (SUV_{max}) was measured using EQ PET software (Siemens, Oxford, UK).

Data Analysis

Qualitative imaging features were independently evaluated by two readers: the first author, a breast surgeon (Reader 1), and a coauthor, a radiologist (Reader 2), with 18 and 19 years of experience in breast imaging, respectively. Disagreements regarding qualitative imaging findings were resolved by consensus. The independent double reading of the mammograms (MMG) was performed retrospectively by two qualified individuals certified by the Central Organization for Quality Assurance of Breast Cancer Screening in Japan. For MMG and ultrasonographic data analysis, all tumors were retrospectively evaluated according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Fifth Edition categories. For MRI data analysis, morphology, internal enhancement

characteristics, internal architecture, and time-signal intensity curve patterns were evaluated on the most representative cross-sectional images, including T2WI and post-contrast enhanced T1WI, selected based on the largest tumor extent. In addition to tumor morphological characteristics assessed by BI-RADS, intratumoral and peritumoral ADC values were evaluated on the ADC maps. Three circular ROIs were placed in each of the intratumoral and peritumoral regions. Each ROI was approximately 5 mm in diameter and included at least three voxels. Intratumoral ROIs were manually placed in solid tumor regions, carefully avoiding necrosis, hemorrhage, and cystic degeneration. The peritumoral region was defined as a 5-mm-wide band immediately outside the tumor margin. Peritumoral ROIs were positioned entirely within this band while avoiding overlap with the tumor, adjacent adipose tissue, blood vessels, skin, and pectoral muscle to minimize partial-volume effects.

For each ROI, the mean ADC value was recorded, and the median of the three ROI mean values was used as the representative intratumoral or peritumoral ADC value. ADC measurements used in the main analyses were performed by Reader 1. To assess interobserver reproducibility, Reader 2 independently repeated intratumoral and peritumoral ADC measurements in the first 35 consecutive participants with evaluable MRI, without access to Reader 1's measurements. ^{18}F -FDG PET/CT images were reviewed by two board-certified nuclear medicine physicians, who manually placed a spherical volume of interest over the entire tumor to determine the SUV_{max} .

To minimize bias, both readers were blinded to participants' clinical data and TIL status, and Reader 2 was also blinded to Reader 1's ADC measurements.

Statistical Analysis

Participants were divided into high- and low-TIL groups. Descriptive statistics are presented as the mean $\pm$ standard deviation for continuous variables and as counts and percentages for categorical variables. Associations of individual clinical and imaging variables with high TIL status were evaluated using univariable logistic regression, and odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Fisher's exact test was used for categorical comparisons where indicated, including comparisons of lymphovascular invasion and MRI system according to TIL status. Continuous variables were compared using unpaired t tests or Mann–Whitney U tests, as appropriate. In an exploratory analysis, intratumoral and peritumoral ADC values were compared according to lymphovascular invasion status using the Mann–Whitney U test. Interobserver reproducibility of intratumoral and peritumoral ADC measurements was evaluated using intraclass correlation coefficients (ICCs) with 95% CIs based on a two-way random-effects, absolute-agreement, single-measurement model.

Multivariable logistic regression analysis was performed to identify variables independently associated with high TIL status. Candidate variables were selected a priori based on biological plausibility, previous literature, clinical relevance, and model stability rather than solely on univariable statistical significance. The primary MRI-based model included intratumoral ADC, peritumoral ADC, and MRI margin. Two additional multivariable models were examined: a histological grade–adjusted model including intratumoral ADC, peritumoral ADC, and histological grade, and an exploratory PET/CT model including

intratumoral ADC, peritumoral ADC, and SUVmax. To assess potential scanner-related heterogeneity, the primary model was repeated with MRI system included as an additional categorical covariate. The primary model was also repeated after restricting the analysis to participants examined using the predominant Ingenia 3.0T system. Multicollinearity was assessed before model fitting. ORs for ADC values were expressed per $0.1 \times 10^{-3} \text{ mm}^2/\text{s}$ increase.

Receiver operating characteristic (ROC) analysis was performed to assess the ability of intratumoral ADC alone and the predicted probabilities from the primary MRI-based model to discriminate between high and low TIL status. The apparent areas under the ROC curve (AUCs) of the primary MRI-based model and intratumoral ADC alone were compared using DeLong's test for correlated ROC curves. The Youden index was used to determine the optimal cutoff value for maximizing sensitivity and specificity. Internal validation of the primary MRI-based model was performed using 1,000 bootstrap resamples. In each bootstrap sample, the model was refitted, and its AUC was calculated both in the bootstrap sample and after application of the bootstrap-fitted model to the original cohort. Optimism was defined as the difference between these two AUCs. The mean optimism across the 1,000 resamples was subtracted from the apparent AUC of the model to obtain the optimism-corrected AUC. No imputation was performed. Each modality-specific analysis and multivariable model was based on participants with complete data for all variables included in that analysis.

For exploratory clinical outcome analyses, pCR rates were compared between TIL groups defined using the 10% and 50% cutoffs using Fisher's exact test. Additional exploratory analyses were performed to evaluate the association between intratumoral ADC and pCR using Fisher's exact test for the ROC-derived ADC cutoff and an unpaired t test for continuous ADC values. Survival outcomes were not analyzed because the number of recurrence and survival events was insufficient for reliable statistical evaluation. All statistical tests were two-sided, and p values < 0.05 were considered statistically significant. Analyses were performed using Python version 3.12.13 with NumPy version 2.3.5, pandas version 2.2.3, SciPy version 1.17.0, and scikit-learn version 1.8.0. DeLong's test and bootstrap internal validation were implemented using custom Python code.

Results

After applying the inclusion and exclusion criteria, 79 participants with TNBC were included in the final analysis (Fig. 1). The demographic and tumor characteristics of these participants are summarized in Table 1.

Table 1
Participant and tumor characteristics (N = 79)

Age		N	(%)
		64 ± 12.9	
Family history	Presence	17	21.5
	Absence	62	78.5
BRCA pathogenic mutation	Presence	11	13.9
	Absence	30	38.0
	Unknown	38	48.1
Body mass index		23 ± 3.6	
Menopausal	Pre	19	24.1
	Post	60	75.9
Clinical T stage	T1a	0	0.0
	T1b	9	11.4
	T1c	22	27.8
	T2	45	57.0
	T3	3	3.8
Clinical N stage	N0	51	64.6
	N1	28	35.4
Clinical stage	Ⅺ	30	38.0
	ⅪA	24	30.4
	ⅪB	22	27.8
	ⅪA	3	3.8
Histological grade	1	15	19.0
	2	24	30.4
	3	30	38.0
	Unknown	10	12.7
Ki-67 index	< 20%	28	35.4
	≥ 20%	51	64.6

Age		N	(%)
		64 ± 12.9	
TILs	< 10%	22	27.8
	≥ 10%	57	72.2
pCR status (N = 56)	Non-pCR	30	53.6
	pCR	26	46.4
Pretreatment imaging	Mammography	79	100.0
	Ultrasonography	79	100.0
	MRI	76	96.2
	¹⁸ F-FDG PET/CT	63	79.7
Values are presented as mean ± standard deviation or n (%). Percentages for pCR status were calculated among evaluable cases (N = 56). All other percentages were calculated using the total cohort (N = 79). Note. BRCA; breast cancer susceptibility gene, pCR; pathological complete response, TIL; tumor-infiltrating lymphocytes, MRI; magnetic resonance imaging, PET/CT; positron emission tomography/computed tomography.			

Among the 79 participants included in the study, 57 (72.2%) were classified as having high TIL levels, whereas 22 (27.8%) were categorized as having low TIL levels. TIL levels ≥ 50% were observed in 22 participants (27.8%). All tested tumors were negative for ER, PgR, and HER2 expression. All participants underwent MMG and ultrasonography, and the corresponding images were reviewed. Additionally, 76 (96.2%) participants underwent pretreatment MRI, and 63 (79.7%) underwent ¹⁸F-FDG PET/CT. Imaging-based analyses were performed using the available data for each modality. pCR was evaluable in 56 participants who underwent neoadjuvant systemic therapy and had available surgical pathology; among these, 26 participants (46.4%) achieved pCR.

The associations of clinical factors and imaging findings with TIL status are summarized in Tables 2 and 3.

Table 2
Univariable associations of clinical and imaging findings with high TIL status ($\geq 10\%$)

Clinical factor		Odds ratio (95% CI)	p value
	Age	0.99 (0.95–1.03)	0.57
	BRCA pathogenic mutation (N = 41)	5.79 (0.65–51.51)	0.12
	Body mass index	1.12 (0.96–1.30)	0.14
	Menopausal state	1.61 (0.47–5.52)	0.45
	Clinical T	1.08 (0.56–2.09)	0.81
	Clinical N	0.72 (0.26–1.99)	0.53
	Clinical Stage	1.04 (0.60–1.79)	0.90
	Ki-67	1.81 (0.66–4.95)	0.25
	Histological grade	1.88 (0.96–3.67)	0.07
	Lymphovascular invasion, presence vs absence (N = 69)	1.05 (0.31–3.52)	1.00
Mammography (N = 79)	Background breast parenchyma	1.63 (0.75–3.55)	0.22
	Presence of mass	1.28 (0.47–3.51)	0.63
	Presence of focal asymmetry	0.64 (0.20–2.01)	0.44
	Presence of calcification	2.03 (0.09–43.91)	1.00
	Presence of distortion	1.63 (0.32–8.37)	0.56
Ultrasonography (N = 79)	Shape	0.69 (0.22–2.18)	0.53
	Margin	0.68 (0.20–2.36)	0.55
	Internal echogenicity	0.63 (0.30–1.34)	0.23
	Posterior echo	1.24 (0.62–2.48)	0.55
DCE-MRI (N = 76)	Shape	0.29 (0.08–1.12)	0.07
	Margin	0.25 (0.07–0.96)	0.04
	Rim enhancement	0.33 (0.11–1.04)	0.06
	Intratumoral T2WI high SI area	0.88 (0.32–2.45)	0.80
	Peritumoral edema	1.20 (0.40–3.62)	0.75
	Intratumoral ADC	4.40 (2.04–9.47)	< 0.01

Clinical factor		Odds ratio (95% CI)	p value
	Age	0.99 (0.95–1.03)	0.57
	Peritumoral ADC	0.54 (0.34–0.86)	< 0.01
¹⁸ F-FDG PET/CT (N = 63)	SUV _{max}	1.36 (1.13–1.64)	< 0.01
Note. TILs; Tumor-Infiltrating Lymphocytes, DCE-MRI; Dynamic contrast-enhanced MRI, T2WI; T2-weighted image, ADC; apparent diffusion coefficient, SUV_{max}; the maximum standardized uptake value. Odds ratios for ADC values are expressed per $0.1 \times 10^{-3} \text{ mm}^2/\text{s}$ increase.			

Table 3
Multivariable logistic regression models for high TIL status ($\geq 10\%$)

Model	Variable	Adjusted odds ratio (95% CI)	p value
Model 1: MRI-based model	Intratumoral ADC	6.96 (2.47–19.67)	< 0.001
	Peritumoral ADC	0.27 (0.11–0.66)	0.004
	MRI margin, not circumscribed vs circumscribed	0.46 (0.08–2.71)	0.394
Model 2: Histological grade-adjusted model	Intratumoral ADC	6.69 (2.31–19.37)	< 0.001
	Peritumoral ADC	0.33 (0.13–0.80)	0.014
	Histological grade	1.84 (0.68–4.98)	0.228
Model 3: PET/CT exploratory model	Intratumoral ADC	11.74 (2.32–59.37)	0.003
	Peritumoral ADC	0.29 (0.10–0.83)	0.021
	SUV _{max}	1.55 (1.06–2.27)	0.024
Note. ADC; apparent diffusion coefficient, CI; confidence interval, MRI; magnetic resonance imaging, PET/CT; positron emission tomography/computed tomography, SUV_{max}; maximum standardized uptake value, TIL; tumor-infiltrating lymphocyte. Odds ratios for ADC values are expressed per $0.1 \times 10^{-3} \text{ mm}^2/\text{s}$ increase. Each model was analyzed using complete cases for the included variables. Model 1 included 76 participants, Model 2 included 66 participants, and Model 3 included 60 participants. Model 3 was considered exploratory because SUV_{max} was available only in participants who underwent ¹⁸F-FDG PET/CT, and three participants with SUV_{max} data lacked evaluable ADC measurements.			

No statistically significant difference in Ki-67 expression was observed between the high- and low-TIL groups. Although histological grade was not significantly associated with TIL status, higher grades tended to be more frequent in the high-TIL group (OR 1.88, 95% CI 0.96–3.67, $p = 0.07$). Other clinical characteristics, including participant age, menopausal status, BRCA1/2 mutation status, clinical stage, and TNM classification, showed no significant differences between the two groups. Lymphovascular invasion was evaluable in 69 participants and was present in 53. It was not associated with high TIL status (OR 1.05, 95% CI 0.31–3.52; $p = 1.00$).

No statistically significant differences were found in the imaging features obtained with MMG or ultrasonography. However, MRI-derived features revealed significant associations with high TIL levels. MRI margin was significantly associated with TIL status (OR 0.25, 95% CI 0.07–0.96, $p = 0.04$). Higher intratumoral ADC values (OR 4.40, 95% CI 2.04–9.47, $p < 0.01$) were significantly associated with the high-TIL group, whereas lower peritumoral ADC values (OR 0.54, 95% CI 0.34–0.86, $p < 0.01$) were also significantly associated with high TIL levels. In an exploratory analysis of the 66 participants with both MRI and lymphovascular invasion data, neither intratumoral nor peritumoral ADC differed significantly according to lymphovascular invasion status ($p = 0.708$ and $p = 0.354$, respectively). Regarding ^{18}F -FDG PET/CT, SUV_{max} was significantly associated with high TIL levels (OR 1.36, 95% CI 1.13–1.64, $p < 0.01$).

Interobserver agreement was high for both ADC parameters. The ICC was 0.891 (95% CI, 0.797–0.943) for intratumoral ADC and 0.823 (95% CI, 0.676–0.907) for peritumoral ADC.

Multivariable logistic regression analysis was performed using three prespecified models (Table 3). In the primary MRI-based model, which included 76 participants, higher intratumoral ADC values remained independently associated with high TIL levels after adjustment for peritumoral ADC and MRI margin (adjusted OR 6.96, 95% CI 2.47–19.67, $p < 0.001$). Lower peritumoral ADC values were also independently associated with high TIL levels (adjusted OR 0.27, 95% CI 0.11–0.66, $p = 0.004$), whereas MRI margin was not significant (adjusted OR 0.46, 95% CI 0.08–2.71, $p = 0.394$).

In the histological grade-adjusted model, which included 66 participants with complete data, the associations of intratumoral ADC (adjusted OR 6.69, 95% CI 2.31–19.37, $p < 0.001$) and peritumoral ADC (adjusted OR 0.33, 95% CI 0.13–0.80, $p = 0.014$) with high TIL levels remained significant, whereas histological grade was not significant.

In the exploratory PET/CT model, which included 60 participants with complete data, intratumoral ADC (adjusted OR 11.74, 95% CI 2.32–59.37, $p = 0.003$), peritumoral ADC (adjusted OR 0.29, 95% CI 0.10–0.83, $p = 0.021$), and SUV_{max} (adjusted OR 1.55, 95% CI 1.06–2.27, $p = 0.024$) were significantly associated with high TIL levels.

Of the 76 participants who underwent MRI, 67 (88.2%) were examined using the Ingenia 3.0T system and 9 (11.8%) using the Vantage Titan system. The proportion of participants with high TIL levels did not differ significantly between the Ingenia and Vantage Titan systems (50/67 [74.6%] vs. 6/9 [66.7%], respectively; $p = 0.691$). In the scanner-adjusted sensitivity analysis, higher intratumoral ADC (adjusted

OR 8.59, 95% CI 2.85–25.94; $p < 0.001$) and lower peritumoral ADC (adjusted OR 0.26, 95% CI 0.10–0.67; $p = 0.005$) remained independently associated with high TIL levels. Similar findings were observed in the analysis restricted to participants examined using the Ingenia 3.0T system: higher intratumoral ADC (adjusted OR 6.93, 95% CI 2.30–20.91; $p < 0.001$) and lower peritumoral ADC (adjusted OR 0.29, 95% CI 0.12–0.72; $p = 0.008$) remained independently associated with high TIL levels.

ROC analysis was performed to assess how well intratumoral ADC values and the predicted probabilities from the primary MRI-based model discriminated between high and low TIL status (Fig. 2). The primary MRI-based model, which included intratumoral ADC, peritumoral ADC, and MRI margin, showed an apparent AUC of 0.934 (95% CI, 0.879–0.989). Bootstrap internal validation demonstrated a mean optimism of 0.020, yielding an optimism-corrected AUC of 0.914. Intratumoral ADC alone showed an AUC of 0.856 (95% CI, 0.768–0.944). The apparent AUC of the primary model was higher than that of intratumoral ADC alone, with an AUC difference of 0.078 (DeLong $p = 0.030$). When a cutoff value of $0.85 \times 10^{-3} \text{ mm}^2/\text{s}$ was applied, the sensitivity and specificity of intratumoral ADC were 83.9% and 80.0%, respectively.

Exploratory analysis of treatment response was performed in participants with evaluable pCR data after neoadjuvant treatment (Table 4). High TIL levels were significantly associated with pCR using both the 10% and 50% cutoffs. Using the 10% cutoff, pCR was achieved in 25 of 43 participants (58.1%) in the high-TIL group, compared with 1 of 13 participants (7.7%) in the low-TIL group (Fisher’s exact $p = 0.001$). Using the 50% cutoff, pCR was achieved in 15 of 19 participants (78.9%) in the high-TIL group and 11 of 37 participants (29.7%) in the low-TIL group (Fisher’s exact $p < 0.001$).

Table 4
Associations of TIL status and intratumoral ADC with pathological complete response

Variable	Group	Non-pCR	pCR	pCR rate	p value
TILs 10% cutoff	Low TIL	12	1	7.7%	0.001
	High TIL	18	25	58.1%	
TILs 50% cutoff	Low TIL	26	11	29.7%	< 0.001
	High TIL	4	15	78.9%	
Intratumoral ADC cutoff	Low ADC < 0.85	11	1	8.3%	0.003
	High ADC ≥ 0.85	18	24	57.1%	
Note. pCR; pathological complete response, TIL; tumor-infiltrating lymphocyte, ADC; apparent diffusion coefficient. p values were calculated using Fisher’s exact test.					
The intratumoral ADC cutoff of 0.85×10^{-3} mm ² /s was derived from ROC analysis for distinguishing high from low TIL status. Analyses of TIL cutoffs were performed in 56 participants with evaluable pCR data, whereas analysis of the intratumoral ADC cutoff was performed in 54 participants with both evaluable pCR and ADC data.					

Using the ROC-derived intratumoral ADC cutoff of $0.85 \times 10^{-3} \text{ mm}^2/\text{s}$ for distinguishing high from low TIL status, high intratumoral ADC values were also significantly associated with pCR. pCR was achieved in 24 of 42 participants (57.1%) in the high-ADC group, compared with 1 of 12 participants (8.3%) in the low-ADC group (Fisher's exact $p = 0.003$). Intratumoral ADC values were significantly higher in participants who achieved pCR than in those who did not, with a mean difference of $0.139 \times 10^{-3} \text{ mm}^2/\text{s}$ (95% CI 0.080–0.198, $p < 0.001$).

Discussion

The results of this study demonstrated that higher intratumoral ADC and lower peritumoral ADC values were independently associated with high stromal TIL status in TNBC. The exploratory primary MRI-based model, which combined intratumoral ADC, peritumoral ADC, and MRI margin, showed good apparent discrimination. After bootstrap correction, the model retained an AUC of 0.914, suggesting limited optimism within the present cohort. However, this performance should not be interpreted as evidence of clinical utility, and external multicenter validation remains necessary.

Previous studies have suggested that scoring ultrasonographic features may predict lymphocyte-predominant breast cancer (LPBC) [10]. However, in this study, no significant correlation was observed between ultrasonographic findings and TIL levels. The objective and quantitative evaluation of hand-held ultrasound images is inherently challenging, and their use as a standalone tool for TIL assessment may be limited. Given these constraints, imaging modalities that offer greater reproducibility and quantification—such as DWI—are preferable. In this study, the quantitative parameters derived from intratumoral and peritumoral ADC values were independently associated with TIL status.

Furthermore, previous research has reported that the SUV_{max} on ^{18}F -FDG PET/CT may be useful for predicting TIL levels in TNBC and HER2-positive breast cancer [17, 18]. Consistent with these reports, our study observed a significant association between SUV_{max} and TIL levels in the univariable analysis, and SUV_{max} also remained significant in the exploratory PET/CT model. However, because PET/CT was performed only in a subset of participants, these findings should be interpreted as exploratory. Importantly, the associations of intratumoral and peritumoral ADC values with high TIL levels remained consistent even after accounting for SUV_{max} . These findings suggest that DWI-derived ADC measurements may provide accessible quantitative imaging correlates of tumor immune activity. The differing associations of SUV_{max} and ADC values with TIL status also highlight the complementary roles of PET and MRI and support further investigation of multimodal imaging approaches for tumor characterization.

Elevated TIL levels have been shown to be useful for predicting treatment response and prognosis in TNBC and HER2-positive breast cancer [2, 6, 7, 19]. However, there is a limited number of studies investigating the correlation between imaging parameters and TIL levels, particularly within these subtypes. Previous studies have also reported associations between ADC values and TIL levels, although the direction and strength of these associations have varied across studies [20–22]. Recently, Gigli et al.

reported that MRI features, including ADC values and enhancement characteristics, may predict TIL levels in breast cancer [15]. However, their study analyzed a mixed-subtype cohort, including luminal, HER2-positive, and TNBC cases, with relatively few TNBC cases. Therefore, their findings may not be sufficient to establish the relationship between MRI findings and TIL levels specifically in TNBC. In contrast, our study focused exclusively on participants with TNBC and demonstrated a clear association between DWI-derived ADC parameters and high TIL levels, reinforcing the clinical relevance of ADC in this specific context.

Although high tumor cellularity generally decreases ADC, ADC reflects the combined effects of malignant and immune cell density, extracellular water, stromal architecture, and necrosis. In TNBC, lymphocytic infiltration and accompanying stromal or interstitial changes may increase intratumoral tissue heterogeneity and extracellular water, potentially contributing to higher intratumoral ADC. Conversely, a compact immune-stromal reaction at the invasive front may contribute to lower peritumoral ADC. In the present cohort, lymphovascular invasion was not associated with TIL status or either ADC parameter, suggesting that lymphovascular invasion alone did not explain the observed ADC pattern. Importantly, both the imaging and pathological assessments, including TIL and lymphovascular invasion evaluations, were performed before systemic therapy, thereby minimizing temporal discordance caused by treatment-related changes. Because tumor cellularity, necrosis, and stromal fibrosis were not quantitatively assessed, these biological mechanisms remain hypothetical.

In HER2-positive breast cancer, histological grade, tumor cellularity, and peritumoral edema on T2WI have been independently associated with high TIL levels [23]. Lee et al. also reported that ADC values were not significant in multivariable analysis for HER2-positive cases but showed a trend in which lower ADC values correlated with higher TIL levels. The opposite direction of the ADC association reported by Lee et al. may reflect subtype-specific differences in tumor cellularity, stromal fibrosis, extracellular matrix composition, and the spatial distribution of immune cells. These discrepancies suggest that imaging correlates of TIL levels may differ across breast cancer subtypes. Future validation studies are needed to determine whether pretreatment MRI features can provide reproducible information about TIL levels in TNBC.

Importantly, the exploratory pCR analysis provided additional clinical context for the present findings. High pathological TIL levels were significantly associated with pCR using both 10% and 50% cutoffs, supporting the clinical relevance of TIL status in this TNBC cohort. Furthermore, high intratumoral ADC values defined by the ROC-derived cutoff for distinguishing high from low TIL status were also significantly associated with pCR. These findings indicate that intratumoral ADC was associated with both pathological TIL status and treatment response in this cohort. However, because the pCR analysis was exploratory and limited to participants with available response data after neoadjuvant treatment, the results should be interpreted cautiously and validated in larger prospective cohorts. Because these measurements were obtained from routinely generated ADC maps without radiomics or additional imaging sequences, the approach may be feasible for evaluation in standard breast MRI workflows. Its

incremental value for treatment selection and patient outcomes requires prospective multicenter assessment.

This study had some limitations. First, it was conducted at a single institution, which may have limited the generalizability of the findings. Second, TIL evaluation was performed by a single pathologist. Although the use of pretreatment biopsy specimens ensured temporal correspondence with imaging, biopsy specimens sample only a limited portion of the tumor and may not fully capture the spatial heterogeneity of the tumor immune microenvironment. Although two 3.0-T MRI systems with different acquisition protocols were used, the associations of intratumoral and peritumoral ADC with high TIL status remained consistent after adjustment for the MRI system and in the analysis restricted to the predominant Ingenia 3.0T system. Nevertheless, the small number of participants examined using the Vantage Titan system limited the precise assessment of device-specific effects. Menstrual cycle timing was not systematically controlled and may have influenced enhancement-related MRI features. However, a previous prospective study found no significant menstrual-phase-related differences in ADC values of either breast cancers or normal fibroglandular tissue, suggesting that the effect on the ADC-based findings was likely limited [24]. Third, as a retrospective study, this research was inherently prone to selection and information biases. To address potential overfitting, we used prespecified multivariable models, sensitivity analyses, and bootstrap internal validation. Nevertheless, the absence of external validation limits the generalizability of the model. Lastly, the sample size was relatively small, with 79 participants included in the analysis. Survival outcomes were not analyzed because the number of recurrence or survival events was insufficient for reliable statistical evaluation. Given the heterogeneity of breast cancer, further studies with larger cohorts are warranted to validate our findings.

Conclusions

Intratumoral and peritumoral ADC measurements on routine pretreatment 3-T breast MRI were independently associated with high stromal TIL status in this single-center TNBC cohort. An exploratory MRI-based model showed good discrimination after bootstrap correction, and intratumoral ADC was associated with pCR. These findings support external evaluation of routine ADC measurements as accessible imaging correlates of the TNBC immune microenvironment; their clinical utility remains to be established.

Abbreviations

¹⁸F-FDG, ¹⁸F-fluorodeoxyglucose; ADC, apparent diffusion coefficient; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DWI, diffusion-weighted imaging; ER, estrogen receptor; FDG, fluorodeoxyglucose; HER2, human epidermal growth factor receptor 2; MMG, mammography; MRI, magnetic resonance imaging; OR, odds ratio; pCR, pathological complete response; PET/CT, positron emission tomography/computed tomography; PgR, progesterone receptor; ROC, receiver operating characteristic; ROI, region of interest;

SUV_{max}, maximum standardized uptake value; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; TIL, tumor-infiltrating lymphocyte.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Tokyo Women's Medical University (approval no. 5069). The Institutional Review Board approved an opt-out approach to informed consent owing to the retrospective design. Study information was disclosed on the institutional bulletin board, and participants were given the opportunity to opt out. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

HT and SA-T conceptualized the study. HT designed the study. HT and JT collected and analyzed the imaging data. HH, YS, MN, AN, and KA collected the clinical data. EN managed the data. YN performed the pathological evaluation, including TIL assessment. JT performed the statistical analyses. SA-T supervised the study. All authors interpreted the results, critically revised the manuscript, and read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because of institutional restrictions and participant confidentiality but are available from the corresponding author on reasonable request and subject to institutional approval.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–49. 10.3322/caac.21660.
2. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol*. 2018;19(1):40–50. 10.1016/S1470-2045(17)30904-X.
3. Stanton SE, Adams S, Disis ML. Variation in the Incidence and Magnitude of Tumor-Infiltrating Lymphocytes in Breast Cancer Subtypes: A Systematic Review. *JAMA Oncol*. 2016;2(10):1354–60. 10.1001/jamaoncol.2016.1061.
4. Loi S, Salgado R, Schmid P, Cortes J, Cescon DW, Winer EP, et al. Association Between Biomarkers and Clinical Outcomes of Pembrolizumab Monotherapy in Patients With Metastatic Triple-Negative Breast Cancer: KEYNOTE-086 Exploratory Analysis. *JCO Precis Oncol*. 2023;7:e2200317. 10.1200/PO.22.00317.
5. Schmid P, Salgado R, Park YH, Munoz-Couselo E, Kim SB, Sohn J, et al. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. *Ann Oncol*. 2020;31(5):569–81. 10.1016/j.annonc.2020.01.072.
6. Loi S, Drubay D, Adams S, Pruneri G, Francis PA, Lacroix-Triki M, et al. Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers. *J Clin Oncol*. 2019;37(7):559–69. 10.1200/JCO.18.01010.
7. Perez EA, Ballman KV, Tenner KS, Thompson EA, Badve SS, Bailey H, et al. Association of Stromal Tumor-Infiltrating Lymphocytes With Recurrence-Free Survival in the N9831 Adjuvant Trial in Patients With Early-Stage HER2-Positive Breast Cancer. *JAMA Oncol*. 2016;2(1):56–64. 10.1001/jamaoncol.2015.3239.
8. Hendry S, Salgado R, Gevaert T, Russell PA, John T, Thapa B, the International Immuno-Oncology Biomarkers Working Group. Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from : Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinomas, Non-Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary

- Carcinomas, and Primary Brain Tumors. *Adv Anat Pathol*. 2017;24(6):311 – 35. 10.1097/PAP.0000000000000161
9. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruner G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Ann Oncol*. 2015;26(2):259–71. 10.1093/annonc/mdu450.
 10. Kimura Y, Masumoto N, Kanou A, Fukui K, Sasada S, Emi A, et al. The TILs-US score on ultrasonography can predict the pathological response to neoadjuvant chemotherapy for human epidermal growth factor receptor 2-positive and triple-negative breast cancer. *Surg Oncol*. 2022;41:101725. 10.1016/j.suronc.2022.101725.
 11. Tang WJ, Kong QC, Cheng ZX, Liang YS, Jin Z, Chen LX, et al. Performance of radiomics models for tumour-infiltrating lymphocyte (TIL) prediction in breast cancer: the role of the dynamic contrast-enhanced (DCE) MRI phase. *Eur Radiol*. 2022;32(2):864–75. 10.1007/s00330-021-08173-5.
 12. Bian T, Wu Z, Lin Q, Mao Y, Wang H, Chen J, et al. Evaluating Tumor-Infiltrating Lymphocytes in Breast Cancer Using Preoperative MRI-Based Radiomics. *J Magn Reson Imaging*. 2022;55(3):772–84. 10.1002/jmri.27910.
 13. Xu N, Zhou J, He X, Ye S, Miao H, Liu H, et al. Radiomics Model for Evaluating the Level of Tumor-Infiltrating Lymphocytes in Breast Cancer Based on Dynamic Contrast-Enhanced MRI. *Clin Breast Cancer*. 2021;21(5):440–e91. 10.1016/j.clbc.2020.12.008.
 14. Dieci MV, Radosevic-Robin N, Fineberg S, van den Eynden G, Ternes N, Penault-Llorca F, et al. Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: A report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer. *Semin Cancer Biol*. 2018;52(Pt 2):16–25. 10.1016/j.semcancer.2017.10.003.
 15. Gigli S, David E, Bonito G, Favale L, di Sero S, Vinci A et al. Role of Preoperative Breast MRI in Predicting Tumor-Infiltrating Lymphocytes in Breast Cancer: Is There an Association with Tumor Biological Subtypes? *Biomedicines*. 2025;13(6):1364. 10.3390/biomedicines13061364
 16. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164–72. 10.1016/S0140-6736(13)62422-8.
 17. Park S, Min EK, Bae SJ, Cha C, Kim D, Lee J, et al. Relationship of the standard uptake value of (18)F-FDG-PET-CT with tumor-infiltrating lymphocytes in breast tumors measuring ≥ 1 cm. *Sci Rep*. 2021;11(1):12046. 10.1038/s41598-021-91404-y.
 18. Murakami W, Tozaki M, Sasaki M, Hida AI, Ohi Y, Kubota K, et al. Correlation between (18)F-FDG uptake on PET/MRI and the level of tumor-infiltrating lymphocytes (TILs) in triple-negative and HER2-positive breast cancer. *Eur J Radiol*. 2020;123:108773. 10.1016/j.ejrad.2019.108773.
 19. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, Shulman LN, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant

- breast cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol*. 2014;32(27):2959–66. 10.1200/JCO.2013.55.0491.
20. Chen S, Sui Y, Ding S, Chen C, Liu C, Zhong Z, et al. A simple and convenient model combining multiparametric MRI and clinical features to predict tumour-infiltrating lymphocytes in breast cancer. *Clin Radiol*. 2023;78(12):e1065–74. 10.1016/j.crad.2023.08.029.
21. Celebi F, Agacayak F, Ozturk A, Ilgun S, Ucuncu M, Iyigun ZE, et al. Usefulness of imaging findings in predicting tumor-infiltrating lymphocytes in patients with breast cancer. *Eur Radiol*. 2020;30(4):2049–57. 10.1007/s00330-019-06516-x.
22. Fogante M, Tagliati C, De Lisa M, Berardi R, Giuseppetti GM, Giovagnoni A. Correlation between apparent diffusion coefficient of magnetic resonance imaging and tumor-infiltrating lymphocytes in breast cancer. *Radiol Med*. 2019;124(7):581–7. 10.1007/s11547-019-01008-w.
23. Lee HJ, Lee JE, Jeong WG, Ki SY, Park MH, Lee JS, et al. HER2-Positive Breast Cancer: Association of MRI and Clinicopathologic Features With Tumor-Infiltrating Lymphocytes. *AJR Am J Roentgenol*. 2022;218(2):258–69. 10.2214/AJR.21.26400.
24. Kim JY, Suh HB, Kang HJ, Shin JK, Choo KS, Nam KJ, et al. Apparent diffusion coefficient of breast cancer and normal fibroglandular tissue in diffusion-weighted imaging: the effects of menstrual cycle and menopausal status. *Breast Cancer Res Treat*. 2016;157(1):31–40. 10.1007/s10549-016-3793-0.

Figures

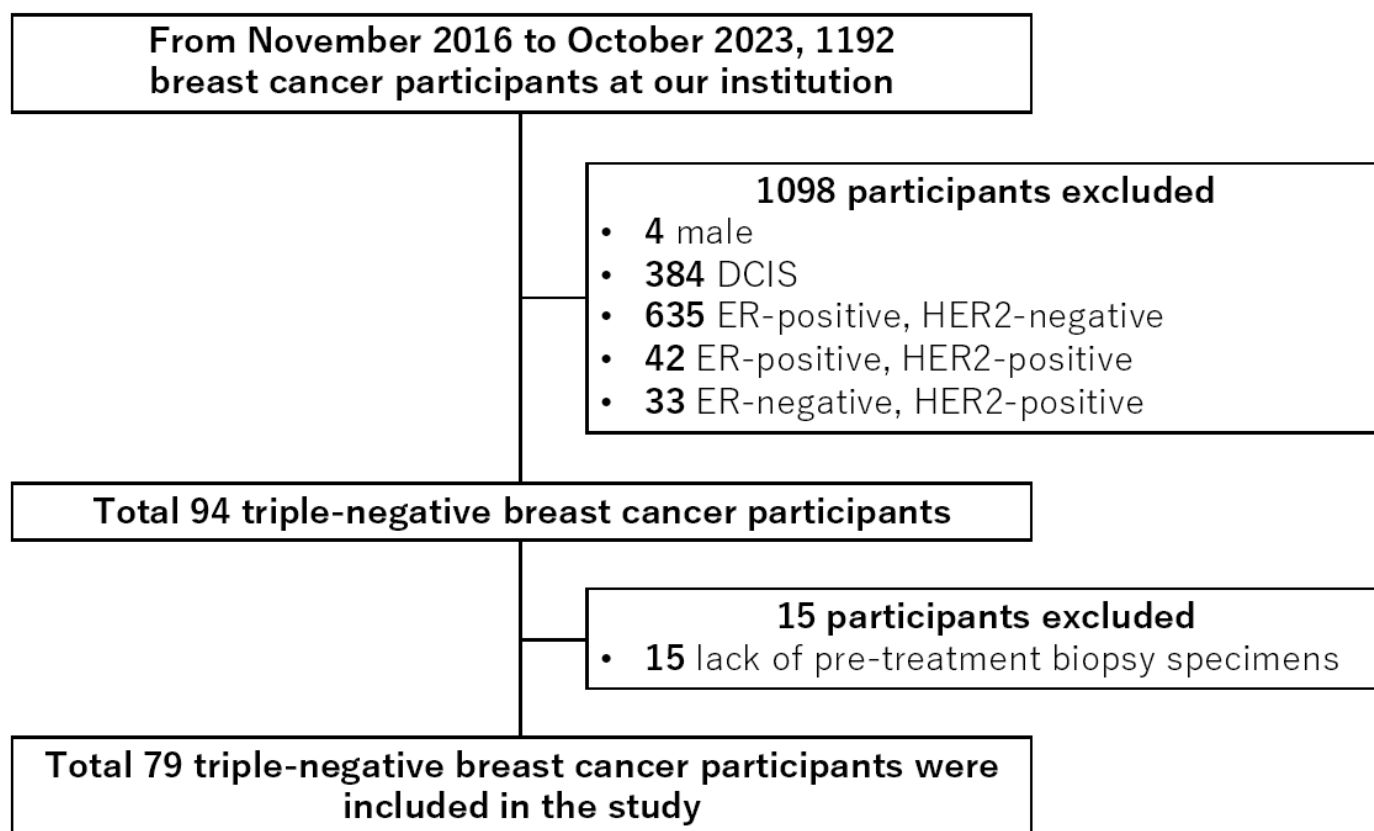


Figure 1

Study flow diagram of participant selection

Flowchart illustrating the selection process of 79 participants with triple-negative breast cancer (TNBC). Out of 1,192 participants initially assessed between November 2016 and October 2023, 1,098 were excluded owing to subtype, diagnosis, or sex. Among 94 TNBC cases, 15 were excluded owing to lack of pretreatment biopsy specimens.

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; DCIS, ductal carcinoma in situ.

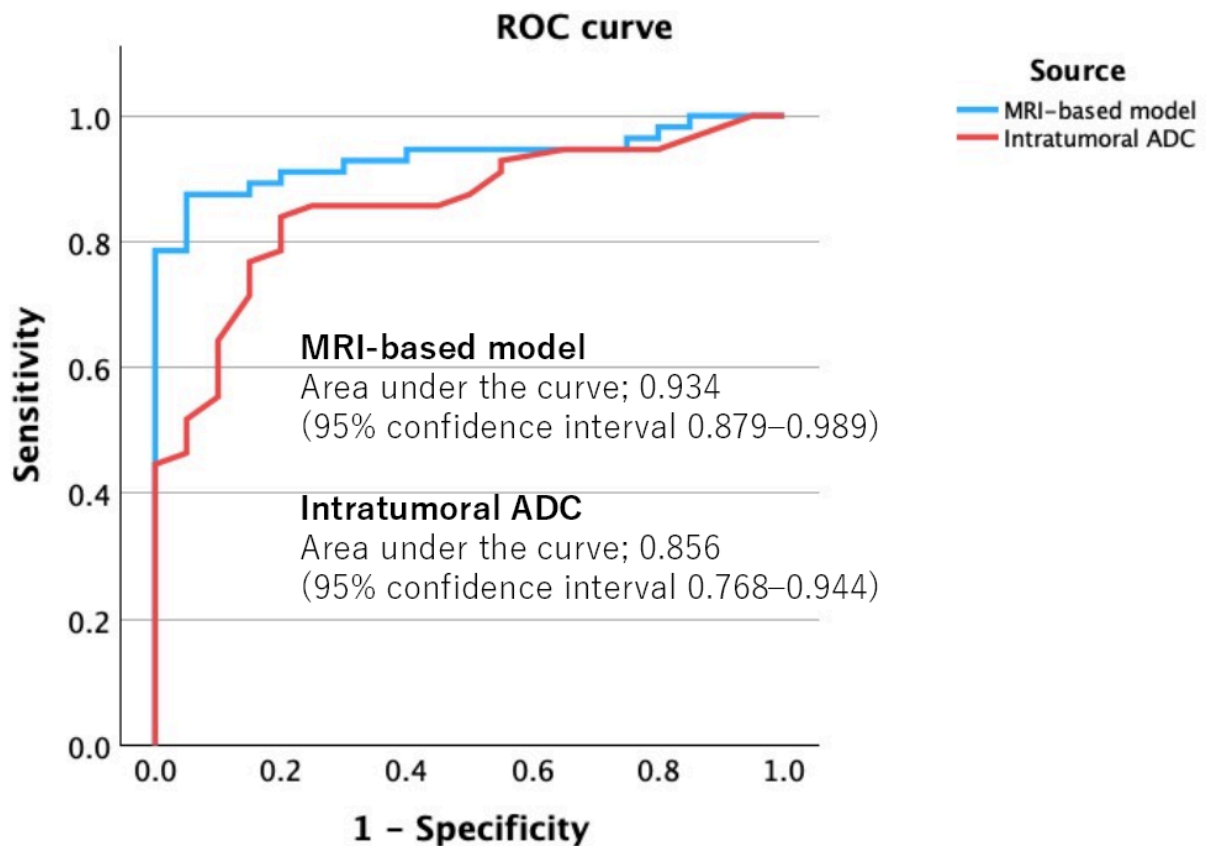


Figure 2

Receiver operating characteristic curves for high TIL status

Receiver operating characteristic (ROC) curves showing the discriminative performance of the primary MRI-based model and intratumoral apparent diffusion coefficient (ADC) alone for distinguishing high from low tumor-infiltrating lymphocyte (TIL) status. The primary model included intratumoral ADC, peritumoral ADC, and MRI margin. Its apparent area under the curve (AUC) was 0.934 (95% confidence interval [CI], 0.879–0.989), and the optimism-corrected AUC after bootstrap internal validation was 0.914. Intratumoral ADC alone had an AUC of 0.856 (95% CI, 0.768–0.944), with sensitivity of 83.9% and specificity of 80.0% at a cutoff of $0.85 \times 10^{-3} \text{ mm}^2/\text{s}$. The difference in apparent AUCs was significant ($\Delta\text{AUC} = 0.078$; DeLong $p = 0.030$).

ADC, apparent diffusion coefficient; AUC, area under the curve; CI, confidence interval; MRI, magnetic resonance imaging; TIL, tumor-infiltrating lymphocyte.