

A Pretreatment Model Integrating IDEAL-IQ–Derived Peritumoral Adipose Metrics for Predicting Pathological Complete Response in Breast Cancer

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Research Article

Keywords: Breast cancer, neoadjuvant chemotherapy, pathological complete response, IDEAL-IQ, peritumoral adipose, imaging biomarker

Posted Date: September 30th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10805516/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Peritumoral adipose tissue may reflect tumor–microenvironment interactions relevant to treatment response. This study evaluated whether IDEAL-IQ-derived fat-fraction metrics provide additional pretreatment information for pathological complete response (pCR) after neoadjuvant chemotherapy (NAC).

Methods

A total of 73 patients with breast cancer who underwent pretreatment MRI with IDEAL-IQ were included. Peritumoral fat fraction (FFp), contralateral fat fraction (FFh), and their difference ($dFF = FFh - FFp$) were measured. Clinical, IDEAL-IQ, and combined logistic regression models were assessed using receiver operating characteristic analysis, calibration, decision-curve analysis, DeLong tests, and 1,000 bootstrap resamples.

Results

Among the 73 patients, 42 (57.5%) achieved pCR. FFp was significantly lower than FFh overall. Compared with the non-pCR group, patients who achieved pCR had higher FFp and lower dFF. In the combined model, HER2 positivity and lower dFF were independently associated with pCR. The combined model had an AUC of 0.911, compared with 0.856 for the clinical model and 0.719 for the dFF-only model. The AUC improvement over the clinical model was not statistically significant (difference, 0.055; $P = 0.061$), whereas the improvement over the dFF-only model was significant (difference, 0.192; $P = 0.002$). The optimism-corrected AUC was 0.890, with a Brier score of 0.140 and calibration slope of 0.824.

Conclusions

IDEAL-IQ–derived peritumoral adipose metrics, particularly dFF, were associated with pCR and may provide information complementary to a parsimonious clinical model. However, the increase in AUC after adding dFF was not statistically significant, and the incremental value of dFF requires external validation.

Background

Neoadjuvant chemotherapy (NAC) plays a significant role in the management of locally advanced and biologically aggressive breast cancer. In addition to downstaging the primary tumor and facilitating surgery, NAC also provides an in vivo assessment of treatment sensitivity. Pathological complete response (pCR) has become an important clinical indicator, as patients who achieve pCR commonly have better long-term outcomes, particularly those with HER2-positive or triple-negative breast cancer [1, 2]. However, accurate pretreatment prediction of pCR remains difficult. Current assessments mainly rely on conventional

clinicopathologic factors, such as tumor size, nodal status, receptor profile, and proliferation markers, but these factors do not fully capture the complexity of the tumor microenvironment or explain interpatient heterogeneity in treatment response [3].

Peritumoral adipose tissue has received increasing attention as an active part of the breast tumor microenvironment. Adipocytes next to the tumor can undergo phenotypic and metabolic changes and develop features of cancer-associated adipocytes (CAAs), including loss of lipid content, inflammatory activation, extracellular matrix remodeling, and close interaction with tumor cells. These changes may influence tumor progression, invasion, and treatment sensitivity [4, 5]. Accordingly, quantitative assessment of peritumoral adipose tissue may provide biologically relevant information beyond tumor imaging features alone [6].

Magnetic resonance imaging (MRI) is well suited for evaluating breast cancer because of its excellent soft tissue contrast and ability to depict both the tumor and surrounding tissue. Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL-IQ) enables accurate measurement of fat fraction by separating water and fat signals, thereby providing a noninvasive means of characterizing adipose tissue composition [7]. Prior studies have suggested that MRI-based assessment of peritumoral adipose tissue may be associated with tumor subtype, histopathologic aggressiveness, and prognosis [8–10].

IDEAL-IQ provides a quantitative measure of tissue fat fraction and may therefore allow direct assessment of tumor-adjacent adipose tissue without high-dimensional feature extraction. We therefore evaluated IDEAL-IQ-derived peritumoral fat-fraction metrics and tested whether dFF provided additional information to a parsimonious clinical model for pretreatment pCR prediction.

Based on these considerations, we hypothesized that quantitative alterations in peritumoral adipose tissue may reflect tumor–adipose interaction relevant to treatment response. Accordingly, this study aimed to evaluate IDEAL-IQ–derived peritumoral adipose metrics in breast cancer patients undergoing NAC and to develop an exploratory pretreatment model for pCR stratification by combining imaging biomarkers with routinely available clinicopathologic factors.

Methods

Study Cohort

This was a prospective, single-center observational cohort study. Consecutive women with biopsy-proven stage II–III breast cancer who were scheduled to receive NAC were screened before treatment between August 2022 and December 2024. This study was approved by the Research Ethics Committee of Fujian Cancer Hospital (Identifier: K2022-149-01), and written informed consent was obtained from all participants. No additional patient sampling or invasive procedures were performed, and all clinical data were anonymized before analysis. Eligible patients were adult women with previously untreated stage IIA–IIIB breast cancer, no contraindications to MRI, no contralateral breast cancer or distant metastases, and available pathological results from pre-treatment biopsy before NAC. Patients were excluded if MRI image

quality was insufficient for peritumoral adipose assessment, breast density precluded adipose evaluation, the lesion showed a non-mass enhancement pattern with an indistinct tumor boundary, or surgery was not performed after NAC.

All included patients underwent pathological biopsy and immunohistochemical analysis before NAC. NAC regimens varied and included anthracycline- and taxane-based chemotherapy, with or without targeted therapy (Trastuzumab + Pertuzumab). After completion of NAC, all patients underwent surgery, including mastectomy with sentinel lymph node biopsy or axillary lymph node dissection. Pathological complete response (pCR) was defined as the absence of residual invasive carcinoma in the breast and all sampled regional lymph nodes (ypT0/is ypN0).

MRI protocol and data assessment

MRI was performed using a 3.0-T scanner (Discovery MR750W, GE Healthcare, Waukesha, WI, USA) with the patient in the prone position and using an eight-channel dedicated bilateral breast coil. Routine imaging sequences included axial T2-weighted imaging (T2WI), axial diffusion-weighted imaging (DWI; $b = 0, 800$, and 1500 s/mm^2), and dynamic contrast-enhanced T1-weighted imaging (T1WI + C). The iterative decomposition of water and fat with echo asymmetry and least-squares estimation quantitation (IDEAL-IQ) sequence was acquired before contrast administration with the following parameters: repetition time, 6.7 ms; echo time, 0.9 ms; slice thickness, 6 mm; field of view, $42 \times 42 \text{ cm}$; matrix, 256×256 ; and acquisition time, 16 seconds.

All IDEAL-IQ measurements were performed by a radiologist with 10 years of experience in breast MRI interpretation. The reader was blinded to pCR status and postoperative pathological results at the time of measurement. Fat fraction (FF) maps were generated from IDEAL-IQ imaging. With reference to contrast-enhanced and T2-weighted images, the slice showing the largest tumor cross-section was selected for analysis; in multifocal disease, the largest lesion was measured. On the FF map, the reader manually placed circular regions of interest (ROIs; approximately 5 mm in diameter) within 2 cm of the tumor margin. ROIs were positioned in the four quadrants surrounding the lesion, with one ROI per quadrant, and were confined to adipose tissue while avoiding fibroglandular tissue and edema. If adipose tissue in a given quadrant was not measurable on the selected slice, an adjacent slice was used. Four size-matched ROIs were also placed in the corresponding quadrants of the contralateral normal breast. The 2-cm peritumoral range was chosen to capture adipose tissue close to the tumor while limiting the inclusion of more distant breast fat. Small circular ROIs, approximately 5 mm in diameter, were used to make the measurements practical and to reduce partial-volume effects from the tumor, fibroglandular tissue, edema, vessels, and imaging artifacts. Four-quadrant sampling was adopted to partially account for spatial heterogeneity around the lesion and to reduce dependence on a single peritumoral measurement site. The measurement workflow is illustrated in Fig. 1. Mean FF values were then calculated for each side and defined as the peritumoral FF (FFp) and contralateral healthy breast FF (FFh). The peritumoral adipose difference was calculated as $dFF = FFh - FFp$.

Interobserver reproducibility was assessed in a randomly selected subset of 20 cases independently evaluated by two radiologists, each with 10 years of experience in breast MRI interpretation, both blinded to

pCR status and postoperative pathology. Interobserver agreement was evaluated using a two-way random-effects model with absolute agreement for single measurements. The interobserver ICCs were 0.923 for FFp, 0.823 for FFh, and 0.906 for dFF, respectively. Intraobserver reproducibility was additionally assessed in the same subset of 20 patients showed excellent agreement. The intraobserver ICCs using a two-way random-effects model were 0.968 for FFp, 0.932 for FFh, and 0.978 for dFF, respectively. Adjacent-slice ROI placement was required in 10/73 patients (13.7%) because measurable peritumoral adipose tissue was insufficient in at least one quadrant on the largest tumor slice.

Statistical Analysis

Statistical analyses were performed using MedCalc Statistical Software version 23.1.6. Additional bootstrap calibration and decision-curve analyses were performed using R version 4.4.2. No formal a priori sample-size calculation was performed because this was an exploratory study, and the sample size was determined by the number of eligible participants enrolled during the study period. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant. Tumor size and dFF were entered as continuous variables, clinical N stage as an ordinal variable, and HER2 status as a binary variable. Classification metrics were calculated using a predicted-probability threshold of 0.50. Univariable analyses were not used for automated variable selection. Continuous variables were assessed for normality using the Shapiro–Wilk test and are presented as mean $\pm$ standard deviation or median (IQR), as appropriate. Comparisons between groups were made using the independent-samples t test or Mann–Whitney U test. Categorical variables are presented as counts (percentages) and were compared using the chi-square test or Fisher’s exact test.

pCR was the primary endpoint. FFp and FFh were compared using the Wilcoxon signed-rank test. Associations between candidate variables and pCR were first evaluated using univariable logistic regression. Three exploratory logistic regression models were constructed: a clinical model including tumor size, clinical N stage, and HER2 status; an IDEAL-IQ model including dFF; and a combined model integrating tumor size, clinical N stage, HER2 status, and dFF. Given the limited sample size, the model was intentionally kept parsimonious. Tumor size, clinical N stage, and HER2 status were selected to represent primary tumor burden, nodal burden, and a major treatment response related biological factor, respectively.

Model discrimination was assessed using ROC curve analysis and AUCs with 95% CIs. AUCs were compared using the DeLong test. For internal validation, bootstrap resampling with 1,000 repetitions was used to estimate optimism-corrected model performance. Calibration was evaluated using calibration plots, the Hosmer–Lemeshow test, and bootstrap-corrected calibration measures where applicable. To improve transparency and reproducibility, we also reported the intercept and regression coefficients in the Supplementary Materials. Because NAC regimen and HER2-targeted therapy may influence pCR, we performed exploratory sensitivity analyses by adding treatment-related variables to the combined model. We also conducted subgroup analyses according to HER2 status to determine whether the association between dFF and pCR remained consistent across different treatment contexts.

For risk stratification, predicted probabilities from the combined model were categorized post hoc using pragmatic thresholds of < 20%, 20%–50%, and > 50%. These cutoffs were chosen pragmatically to illustrate differences in observed pCR rates rather than to define validated clinical decision thresholds. A predicted probability below 20% was considered low, 20%–50% represented an intermediate and more uncertain range, and a probability above 50% indicated that pCR was more likely than non-pCR. These categories were intended to aid interpretation of the model output and were not proposed as definitive clinical decision thresholds.

Results

Patient characteristics

Between August 2022 and December 2024, 220 consecutive patients scheduled to receive NAC were prospectively screened. After application of the eligibility criteria, 73 patients were included in the final analysis. Among them, 42 (57.5%) achieved pathological complete response (pCR), whereas 31 (42.5%) did not. Baseline clinicopathologic characteristics are summarized in Table 1. The pCR group had a higher proportion of HER2-positive tumors than the non-pCR group (76.2% vs. 16.1%, $P < 0.001$). Clinical T-stage, molecular-subtype, and Ki-67 distributions also differed significantly between the pCR and non-pCR groups ($P = 0.022$, 0.003 , and 0.037 , respectively).

Table 1
Baseline clinicopathologic characteristics of the study cohort according to pCR

Variable	Overall (n = 73)	pCR (n = 42)	Non-pCR (n = 31)	P value
Age, years	49.0 (43.0–57.0)	49.0 (42.2–57.0)	50.0 (43.0–54.5)	0.663
Tumor size, cm	2.6 (2.1–3.4)	2.6 (2.1–3.2)	2.8 (2.2–4.0)	0.214
Clinical T stage, n (%)				0.022
T1	12 (16.4%)	3 (7.1%)	9 (29.0%)	
T2	49 (67.1%)	34 (81.0%)	15 (48.4%)	
T3	6 (8.2%)	2 (4.8%)	4 (12.9%)	
T4	6 (8.2%)	3 (7.1%)	3 (9.7%)	
Clinical N stage, n (%)				0.201
N0	11 (15.1%)	8 (19.0%)	3 (9.7%)	
N1	33 (45.2%)	20 (47.6%)	13 (41.9%)	
N2	21 (28.8%)	12 (28.6%)	9 (29.0%)	
N3	8 (11.0%)	2 (4.8%)	6 (19.4%)	
Clinical stage, n (%)				0.094
Stage II	42 (57.5%)	28 (66.7%)	14 (45.2%)	
Stage III	31 (42.5%)	14 (33.3%)	17 (54.8%)	
Molecular subtype, n (%)				0.003
Luminal A	7 (9.6%)	1 (2.4%)	6 (19.4%)	
Luminal B	39 (53.4%)	22 (52.4%)	17 (54.8%)	
HER2-enriched	20 (27.4%)	17 (40.5%)	3 (9.7%)	
Triple-negative	7 (9.6%)	2 (4.8%)	5 (16.1%)	
ER positive, n (%)	44 (60.3%)	21 (50.0%)	23 (74.2%)	0.053
PR positive, n (%)	38 (52.1%)	20 (47.6%)	18 (58.1%)	0.478
HER2-positive, n (%)	37 (50.7%)	32 (76.2%)	5 (16.1%)	< 0.001
Ki-67 high ($\geq 11\%$), n (%)	66 (90.4%)	41 (97.6%)	25 (80.6%)	0.037

Continuous variables are presented as median (IQR), and categorical variables are presented as n (%). Between-group comparisons were performed using the Mann–Whitney U test, chi-square test, or Fisher’s exact test, as appropriate.

IDEAL-IQ–derived adipose metrics

IDEAL-IQ–derived adipose metrics are shown in Table 2. FFp was lower than FFh in the overall cohort (78.3 vs. 91.4, $P < 0.001$). Patients who achieved pCR had higher FFp than those who did not (80.9 vs. 75.9, $P = 0.002$), whereas FFh did not differ significantly between groups (90.7 vs. 92.0, $P = 0.278$). dFF was lower in the pCR group (9.75 vs. 16.8, $P = 0.002$). Although lower dFF was associated with pCR, substantial overlap remained between the two groups (Fig. 2).

Table 2
IDEAL-IQ–derived adipose metrics in the overall cohort and according to pCR

Parameter	Overall (n = 73)	pCR (n = 42)	Non-pCR (n = 31)	P value
FFp	78.3 (74.9–83.2)	80.9 (77.6–84.0)	75.9 (71.3–79.8)	0.002
FFh	91.4 (89.7–94.6)	90.7 (90.0–93.7)	92.0 (87.7–94.9)	0.278
dFF	10.7 (8.1–17.9)	9.75 (6.53–13.05)	16.8 (9.1–22.0)	0.002

Univariable logistic regression

Among clinicopathologic variables, HER2 positivity was strongly associated with pCR (OR 16.64, 95% CI 5.05–54.79, $P < 0.001$). High Ki-67 expression was also associated with pCR (OR 9.84, 95% CI 1.12–86.59, $P = 0.039$), whereas ER positivity was inversely associated with pCR (OR 0.35, 95% CI 0.13–0.95, $P = 0.040$). Baseline tumor size and clinical N stage were not statistically significant in the univariable models (tumor size: OR 0.64, $P = 0.086$; N stage: OR 0.58, $P = 0.062$). Among IDEAL-IQ parameters, both FFp and dFF were significantly associated with pCR, whereas FFh was not. Because FFp and dFF are mathematically related, they were not included in the same multivariable model. dFF was chosen as the main IDEAL-IQ predictor because it uses the contralateral breast as an internal reference and more directly reflects the local difference in fat fraction between peritumoral and healthy adipose tissue. ER and Ki-67, although associated with pCR in univariable analysis, were not included in the primary model because of their overlap with subtype-related information and the potential for model instability with additional predictors. Sensitivity analyses showed that the association between dFF and pCR remained stable after additional adjustment for ER or Ki-67. dFF remained independently associated with pCR after inclusion of ER (OR 0.830, 95% CI 0.733–0.940; $P = 0.003$) or Ki-67 (OR 0.845, 95% CI 0.751–0.951; $P = 0.005$), without materially altering the primary model findings.

Multivariable prediction models

To assess the incremental predictive value of IDEAL-IQ–derived peritumoral adipose metrics, three prespecified logistic regression models were constructed (Table 3). Model 1, the clinical model, included tumor size, clinical N stage, and HER2 status. In this model, HER2 positivity remained independently associated with pCR (OR 17.0, 95% CI 4.87–59.70, $P < 0.001$), whereas tumor size and N stage were not independently significant. Model 2, the IDEAL-IQ model, included dFF alone, which remained significantly associated with pCR (OR 0.88, 95% CI 0.82–0.95, $P = 0.002$). In Model 3, the combined model, HER2 positivity (OR 23.2, 95% CI 5.11–105.0, $P < 0.001$) and lower dFF (OR 0.84, 95% CI 0.75–0.95, $P = 0.004$) remained associated with pCR after adjustment for tumor size and clinical N stage.

Table 3
Multivariable logistic regression models for predicting pCR.

Variable	Model 1: Clinical model OR (95% CI)	P value	Model 2: IDEAL-IQ model OR (95% CI)	P value	Model 3: Combined model OR (95% CI)	P value
Tumor size	0.617 (0.319–1.190)	0.150	—	—	0.559 (0.283–1.100)	0.094
Clinical N stage	0.559 (0.266–1.170)	0.125	—	—	0.570 (0.258–1.260)	0.165
HER2-positive	17.000 (4.870–59.700)	< 0.001	—	—	23.200 (5.110–105.000)	< 0.001
dFF	—	—	0.883 (0.817–0.954)	0.002	0.841 (0.747–0.946)	0.004
Model discrimination, calibration, and decision-curve analysis						

The diagnostic performance of the three models is compared in Table 4 and illustrated in Fig. 3. The combined model had the highest apparent AUC (0.911, 95% CI 0.827–0.972), compared with 0.856 (95% CI 0.750–0.945) for the parsimonious clinical model and 0.719 (95% CI 0.583–0.843) for the dFF-only model. The AUC difference between the combined and clinical models was 0.055 and did not reach statistical significance ($P = 0.061$), whereas the combined model significantly outperformed the dFF-only model (difference = 0.192, $P = 0.002$). Thus, the present data do not demonstrate a clear improvement in discrimination from adding dFF to the selected clinical variables.

Table 4
Apparent predictive performance of the three models

Model	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	Brier score	Hosmer–Lemeshow P
Model 1: Clinical model	0.856 (0.750–0.945)	0.857	0.806	0.857	0.806	0.836	0.145	0.322
Model 2: IDEAL-IQ model	0.719 (0.583–0.843)	0.905	0.548	0.731	0.810	0.753	0.201	0.371
Model 3: Combined model	0.911 (0.827–0.972)	0.857	0.871	0.900	0.818	0.863	0.115	0.096

Bootstrap internal validation with 1,000 resampling iterations was performed for the combined model, of which 996 samples were successfully fitted. Bootstrap correction reduced the AUC from 0.911 to 0.890 and increased the Brier score from 0.115 to 0.140. The corrected calibration intercept and slope were 0.052 and 0.824, respectively, indicating modest optimism in the apparent model performance. The apparent calibration plot showed reasonable agreement between predicted and observed probabilities (Fig. 4).

Decision-curve analysis showed only modest differences in estimated net benefit between the combined and clinical models across the examined threshold range (Fig. 5).

Sensitivity analyses for treatment heterogeneity

Because HER2 status and treatment regimens may substantially influence pCR, exploratory sensitivity analyses were performed to assess whether the association between dFF and pCR remained consistent after accounting for treatment heterogeneity. When targeted regimen exposure was added to the combined model, dFF remained significantly associated with pCR (OR 0.831, 95% CI 0.734–0.940, $P = 0.003$). Similarly, when NAC regimen was entered as a categorical variable, the association between dFF and pCR remained directionally consistent and statistically significant (OR 0.836, 95% CI 0.723–0.968, $P = 0.016$). In HER2 status subgroup analyses, dFF showed a consistent inverse association with pCR in both HER2-positive and HER2-negative patients, although the adjusted association in the HER2-negative subgroup was borderline after adjustment for tumor size and clinical N stage. The same inverse trend was also maintained after accounting for treatment exposure. However, the subgroup estimates were imprecise, particularly in HER2-positive patients, and the study was not powered to determine whether the effect of dFF differed according to HER2 status.

Risk stratification performance

To assess the interpretability of the predicted probabilities, the combined model was used to stratify patients into low-, intermediate-, and high-probability groups according to their predicted probability of pCR. The observed pCR rate increased from 6.7% in the low-probability group to 27.8% in the intermediate-probability group and 90.0% in the high-probability group. This increasing gradient suggests that the model-derived probabilities may provide an interpretable framework for exploratory pretreatment pCR stratification.

Discussion

In this prospective single-center cohort, peritumoral FFp was lower than contralateral FFh, and lower dFF was associated with pCR after neoadjuvant treatment. The association with dFF persisted after adjustment for tumor size, clinical N stage, and HER2 status. The combined model had an apparent AUC of 0.911 and an optimism-corrected AUC of 0.890; however, its AUC was not significantly higher than that of the parsimonious clinical model (difference = 0.055, $P = 0.061$). The main finding of this study is therefore an association between dFF and treatment response, whereas the incremental predictive value of dFF remains uncertain.

NAC not only downstages tumors and facilitates surgery but also provides an *in vivo* assessment of treatment sensitivity. Standardized definitions of neoadjuvant efficacy endpoints have emphasized the clinical relevance of pCR assessment in breast cancer trials [11]. However, pretreatment prediction of pCR remains challenging when relying on conventional clinicopathologic factors alone. Although tumor size, nodal status, receptor profile, and proliferation markers are informative, their predictive performance is limited by biologic heterogeneity, assay variability, and subtype-specific interactions [12]. Even among

tumors with the same receptor-defined subtype, treatment sensitivity can vary substantially, suggesting that additional biomarkers reflecting the tumor microenvironment may improve pretreatment risk stratification. Prior work suggests that peritumoral imaging features may partly reflect this difference [13]. In HER2-positive breast cancer, for example, peritumoral MRI radiomic signatures have been associated with the HER2-enriched subtype and with pCR after HER2-targeted neoadjuvant therapy. Peritumoral adipose tissue is also increasingly recognized as an active part of the tumor microenvironment rather than simply surrounding tissue. Adipokines and other bioactive mediators, including leptin, adiponectin, and resistin, may influence tumor progression and therapy sensitivity, particularly in aggressive subtypes such as TNBC and HER2-positive disease [8, 14, 15]. Consistently, adipose tissue invasion has been associated with poorer prognosis in TNBC and may also affect chemosensitivity [16].

Reviews on obesity and the breast cancer microenvironment describe adipose tissue as an endocrine/metabolic and immune-modulating organ that can influence cancer progression and therapy sensitivity via cytokines, nutrient supply, immune recruitment, and matrix remodeling [17–19]. Adipocytes adjacent to invasive breast cancer may undergo phenotypic and metabolic reprogramming into cancer-associated adipocytes, characterized by lipid depletion, inflammatory activation, and altered crosstalk with tumor cells [20–22]. These observations provide a biologic basis for imaging-derived assessment of peritumoral adipose tissue. Indeed, accumulating evidence suggests that quantitative evaluation of peritumoral adipose tissue and peritumoral radiomic features can provide additive information beyond tumor-centered imaging alone [3, 23–27]. Taken together, these data support the hypothesis that imaging visible alterations in tumor-adjacent adipose tissue may reflect microenvironmental states relevant to chemotherapy response.

Within this biologic and imaging framework, our findings can be interpreted in the context of cancer-associated adipocytes (CAAs) as an active component of the tumor microenvironment. From an imaging perspective, a reduced peritumoral fat fraction may therefore represent an imaging correlate of local adipose alteration, including edema, inflammatory infiltration, and adipocyte dedifferentiation [24, 28]. In this context, peritumoral adipose tissue represents a plausible biomarker for pretreatment response prediction. In theory, tumor-adjacent adipocytes can transition to inflammatory CAAs and alter cytokine/adipokine signaling and the immune milieu, thereby influencing tumor behavior and treatment response [29]. In addition, adipocytes and lipid metabolic reprogramming may modify drug response and contribute to treatment resistance [30]. However, because spatially matched histopathological samples were unavailable, dFF should be regarded as an imaging correlate of the tumor–adipose environment rather than evidence of a specific cellular or molecular mechanism.

These findings are broadly consistent with prior multimodality literature showing the relevance of peritumoral adipose tissue across CT, PET/CT, and MRI. CT-based fat attenuation, PET/CT-derived peritumoral adipose metabolism or texture, and MRI-based quantitative fat or lipid composition assessments have all been associated with tumor aggressiveness, nodal status, prognosis, or treatment response [9, 10, 23, 26, 31, 32]. Previous predictive studies have shown that combining intratumoral and peritumoral information, or integrating imaging features with clinicopathologic factors, can improve model performance compared with relying on a single source of information. Within this context, dFF has a

somewhat different methodological role from previously reported peritumoral radiomic, DCE-MRI, PET/CT, and IDEAL-based adipose biomarkers. Peritumoral radiomic features derived from DCE-MRI or other sequences can capture spatial heterogeneity at the tumor–host interface, but they often require whole lesion segmentation, image preprocessing, feature extraction, feature selection, and model harmonization. PET/CT-derived peritumoral adipose features provide metabolic information, but they depend on additional nuclear medicine imaging and may reflect glucose metabolism or inflammatory activity rather than fat composition directly. By contrast, IDEAL-IQ–derived dFF is a low-dimensional quantitative fat-fraction metric that directly compares peritumoral adipose tissue with contralateral healthy breast adipose tissue within the same patient. This internal reference may reduce interindividual variability in baseline adipose composition and allows dFF to reflect localized tumor-associated adipose alteration. Therefore, adding dFF to key clinicopathologic variables yielded an interpretable model with numerically higher discrimination, acceptable calibration, and modest differences in estimated net benefit compared with the clinical model. The association between dFF and pCR persisted after adjustment for HER2 status, although this does not establish a distinct microenvironmental mechanism.

Recent studies further suggest that the optimal peritumoral range may be task-specific, with some reports identifying ranges of approximately 6 mm as yielding high predictive performance [3, 25, 27]. The definition of the peritumoral region is not standardized across breast MRI studies, and different ROI strategies likely interrogate different aspects of the tumor microenvironment. Prior radiomics studies have used narrow peritumoral shells of approximately 2–5 mm, whereas others have systematically compared wider expansions up to 8–9 mm and shown that the optimal thickness is not universal but depends on the clinical task. Our 2-cm region should be regarded as a sampling zone for discrete adipose ROIs rather than a continuous 2-cm peritumoral shell. In general, thinner rims may better reflect the immediate tumor–host interface, including invasion, stromal reaction, angiogenic change, and immune infiltration, whereas broader rims may capture a more diffuse field effect but at the cost of including more uninvolved surrounding tissue [33]. Our fat-only ROI strategy was therefore selected to match the biologic focus of this study, namely quantitative assessment of peritumoral adipose alteration rather than broad peritumoral texture characterization.

From a clinical perspective, the value of the proposed model lies not merely in its AUC, but in its ability to provide interpretable pretreatment risk stratification using a small number of routinely available variables. In our study, patients in the low-probability group had an observed pCR rate of only 6.7%, whereas those in the high-probability group had a pCR rate of 90.0%. However, these cutoffs were selected pragmatically and evaluated in the same cohort used to develop the model. They should therefore be viewed as a descriptive illustration of model output rather than as clinically validated risk categories. The practical appeal of dFF lies mainly in its simple within-patient calculation rather than in the current risk thresholds. Whether this measurement improves clinical decision-making requires prospective external validation. While many imaging-based prediction studies in breast cancer increasingly rely on high-dimensional radiomics or complex machine-learning pipelines, radiomics still faces challenges related to generalizability, interpretability, and practical implementation [34]. In contrast, dFF is a simple within-patient quantitative measure that does not require whole-lesion segmentation or high-dimensional feature extraction. Using the contralateral breast as an internal reference may also help reduce variation in baseline adipose composition

between patients. This simpler workflow may make dFF easier to translate into practice, although IDEAL-IQ acquisition and manual ROI placement are still required.

There are several limitations to this study. First, this was a single-center study with a relatively small sample size, with only 73 of the 220 screened patients ultimately included. Excluding patients with limited measurable peritumoral adipose tissue, dense breasts, or non-mass enhancement may have introduced selection bias and reduced the generalizability of our findings. Second, treatment regimens were heterogeneous. Although this reflects real-world practice, regimen variability may have influenced pCR rates. In particular, because HER2 status is closely linked to treatment strategy and pCR probability, part of its strong predictive effect may reflect regimen-related differences. Although sensitivity analyses suggested that the association between dFF and pCR was directionally preserved after accounting for treatment information, the sample size was insufficient for definitive regimen-stratified modeling. Future studies should validate the model in cohorts with standardized treatment protocols or adequate subtype- and regimen-specific analyses. Third, the current analysis was restricted to a pretreatment cross-sectional measurement of peritumoral adipose tissue. Whether dynamic changes in FFp or dFF during NAC provide additional predictive value remains uncertain. In our earlier pilot observations, post-treatment peritumoral fat measurements showed substantial heterogeneity across quadrants, which made objective assessment difficult and suggests that longitudinal adipose biomarkers may require more standardized acquisition and timing strategies. Fourth, the 2-cm ROI sampling zone, the use of adjacent slices in some patients, and manual ROI placement were pragmatic choices that were not optimized or externally validated. Fifth, spatially matched histopathological data were not available to determine the biological basis of dFF. Finally, the model was internally validated only and the study focused on pCR rather than long-term outcomes.

Future studies should validate this model in larger independent cohorts, ideally through multicenter studies with more consistent imaging protocols and treatment pathways. Such studies should standardize treatment exposure and IDEAL-IQ acquisition, evaluate alternative sampling strategies, and determine whether dFF adds reproducible value to a prespecified clinical benchmark.

Conclusion

Our findings suggest that IDEAL-IQ–derived peritumoral adipose measurements, particularly dFF, were associated with pCR in this prospective cohort. Adding dFF to the parsimonious clinical model increased the apparent AUC from 0.856 to 0.911, but this difference was not statistically significant. dFF should therefore be considered an exploratory adjunct imaging marker until its incremental value is confirmed in independent cohorts.

Abbreviations

MRI Magnetic Resonance Imaging

IDEAL Iterative Decomposition of Water and Fat with Echo Asymmetry

NAC Neoadjuvant Chemotherapy

CAAs Cancer-Associated Adipocytes

pCR Pathological complete response

FF fat fraction

HER2 Human Epidermal Growth Factor Receptor 2

ER Estrogen Receptor

PR Progesterone Receptor

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Fujian Cancer Hospital Research Ethics Committee (Approval No. K2022-149-01). Written informed consent was obtained from all participants.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request. The data are not publicly available because they contain potentially identifiable clinical and imaging information and are subject to institutional privacy restrictions.

Competing interests

The authors declare no competing interests.

Funding

This study was funded by Startup Fund for Scientific Research, Fujian Medical University (2021QH1149) and the Joint Funds for the Innovation of Science and Technology, Fujian Province (2023Y9440).

Authors' contributions

XL conceptualized the study, performed image data collection, statistical analysis, and drafted the manuscript. DZ and LS assisted with MRI protocol implementation and data processing. ZH contributed to

statistical design and analysis interpretation. DH supervised the study, contributed to study design, and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

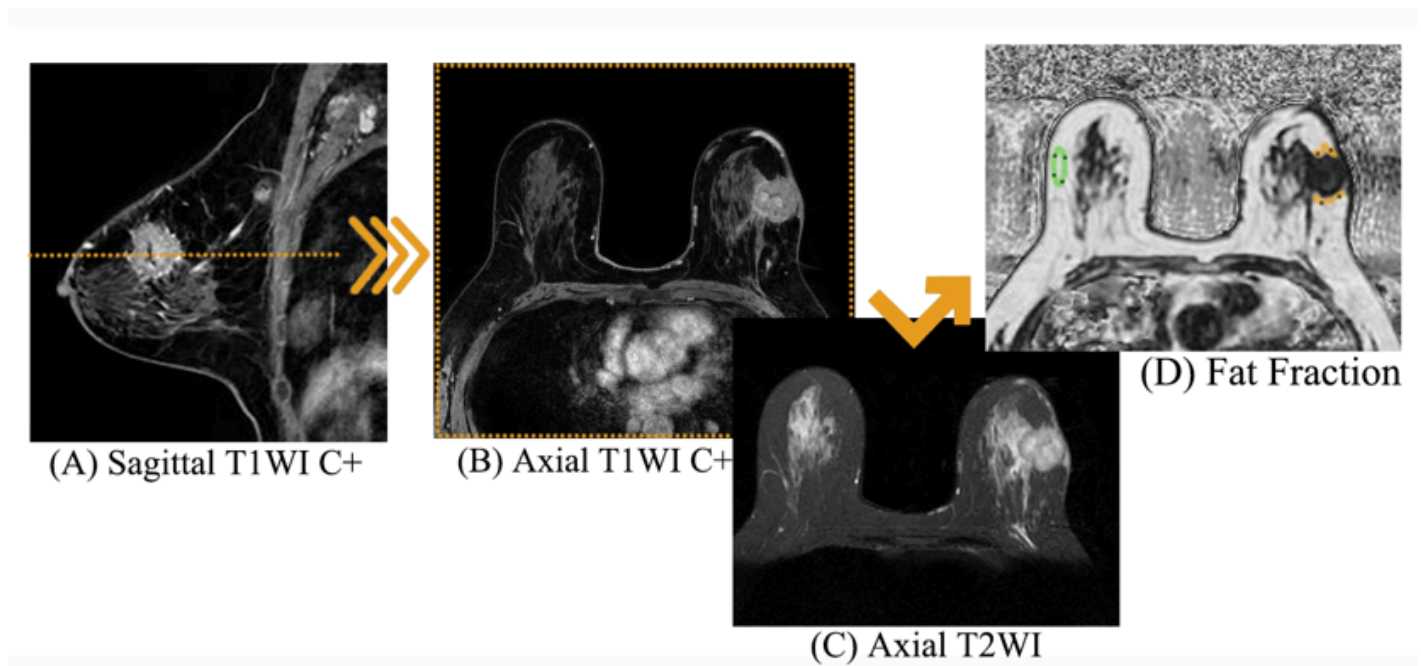


Figure 1

The workflow of FF measurement. The slice showing the largest tumor cross-sectional area was selected (A). With reference to contrast-enhanced and T2-weighted images (B, C), four ROIs for FF measurement (small black circles) were placed in adipose tissue within 2 cm of the tumor margin (yellow area in D), while avoiding fibroglandular tissue and edema. Four corresponding ROIs (small black circles) were also placed in the contralateral normal breast (green area in D).

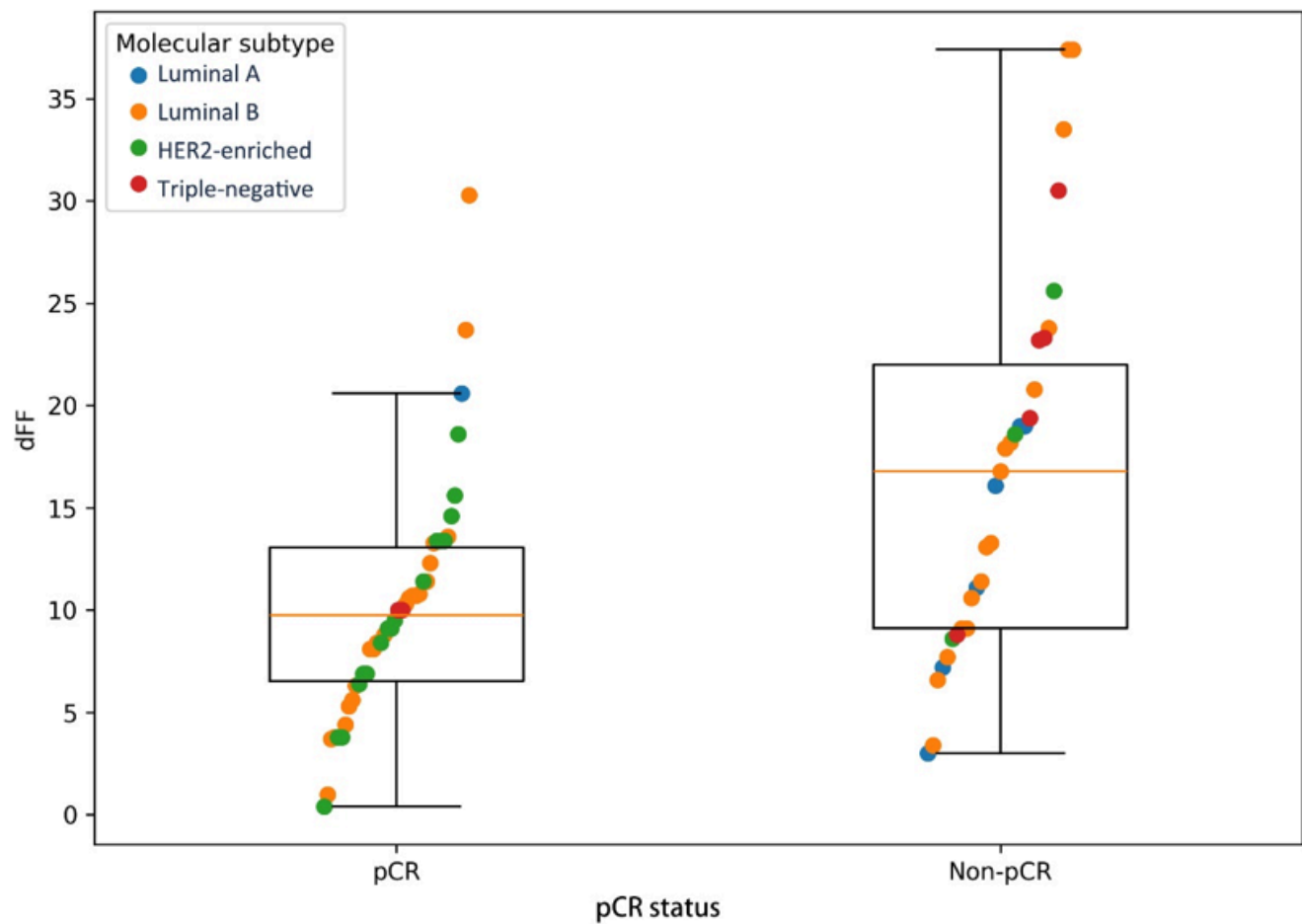


Figure 2

Distribution of dFF according to pathological complete response status with boxplot overlay, colored by molecular subtype. Boxplots summarize the distribution of the fat fraction difference (dFF) in the pCR and non-pCR groups, while each point represents an individual patient. Patients who achieved pCR tended to show lower dFF values than those who did not, although overlap between groups was present.

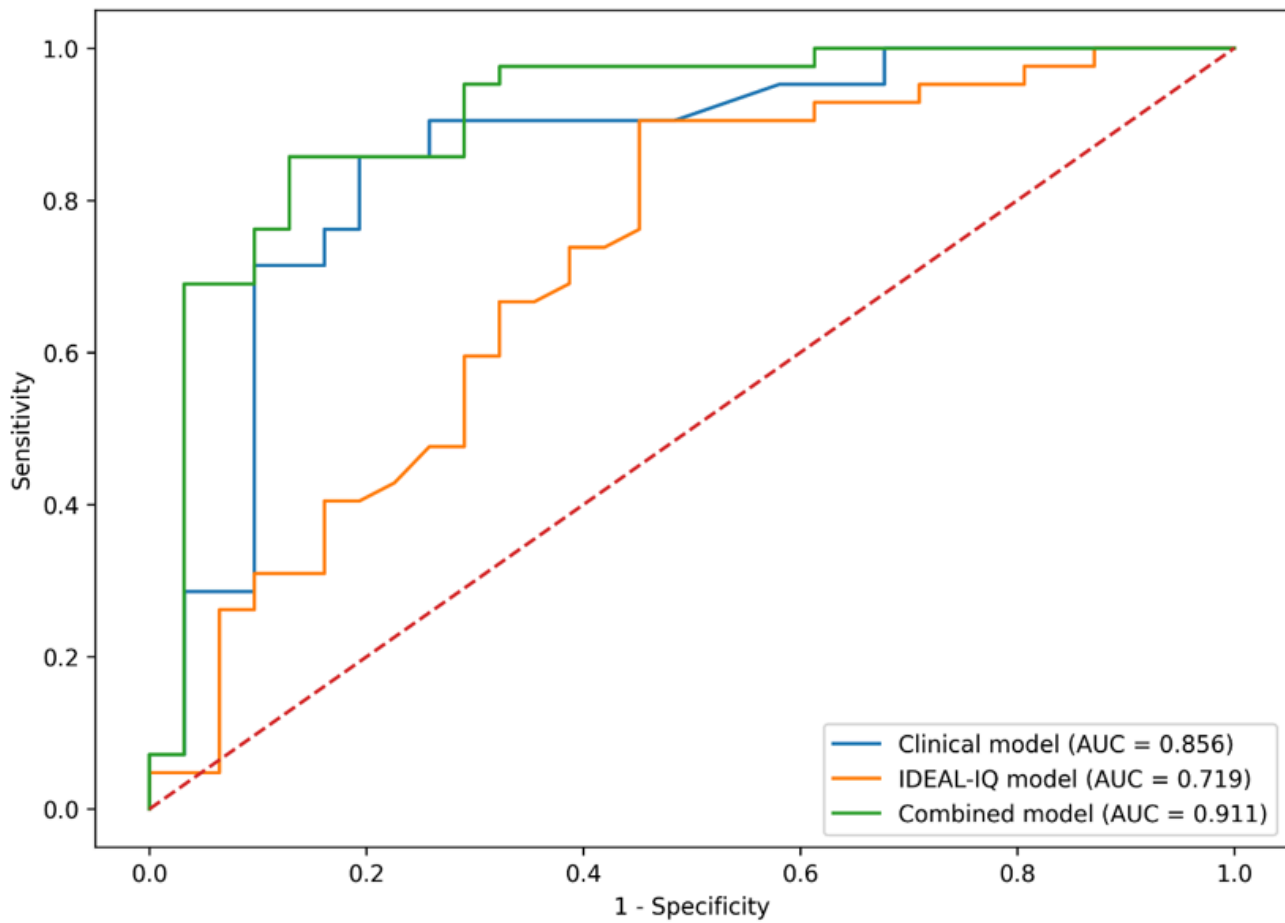


Figure 3

Receiver operating characteristic (ROC) curves of the clinical, IDEAL-IQ, and combined models for predicting pathological complete response. The combined model showed the highest apparent AUC among the three models.

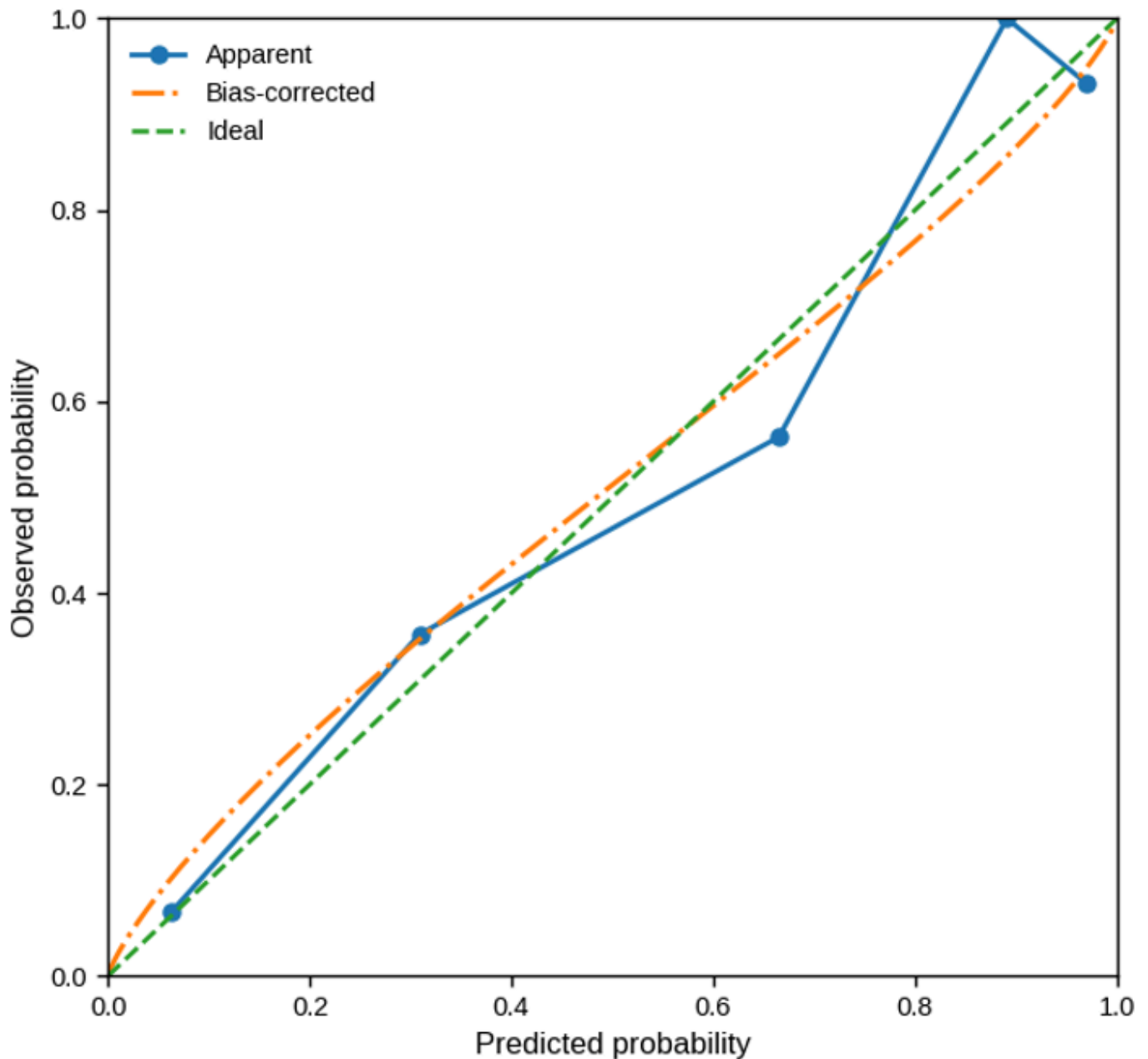


Figure 4

Corrected logistic calibration of the combined model for predicting pathological complete response. The apparent calibration curve was based on grouped predicted and observed probabilities. The orange line represents the logistic calibration relationship implied by the bootstrap-corrected intercept (0.052) and slope (0.824), rather than a pointwise bootstrap-smoothed calibration curve. The diagonal line represents ideal calibration.

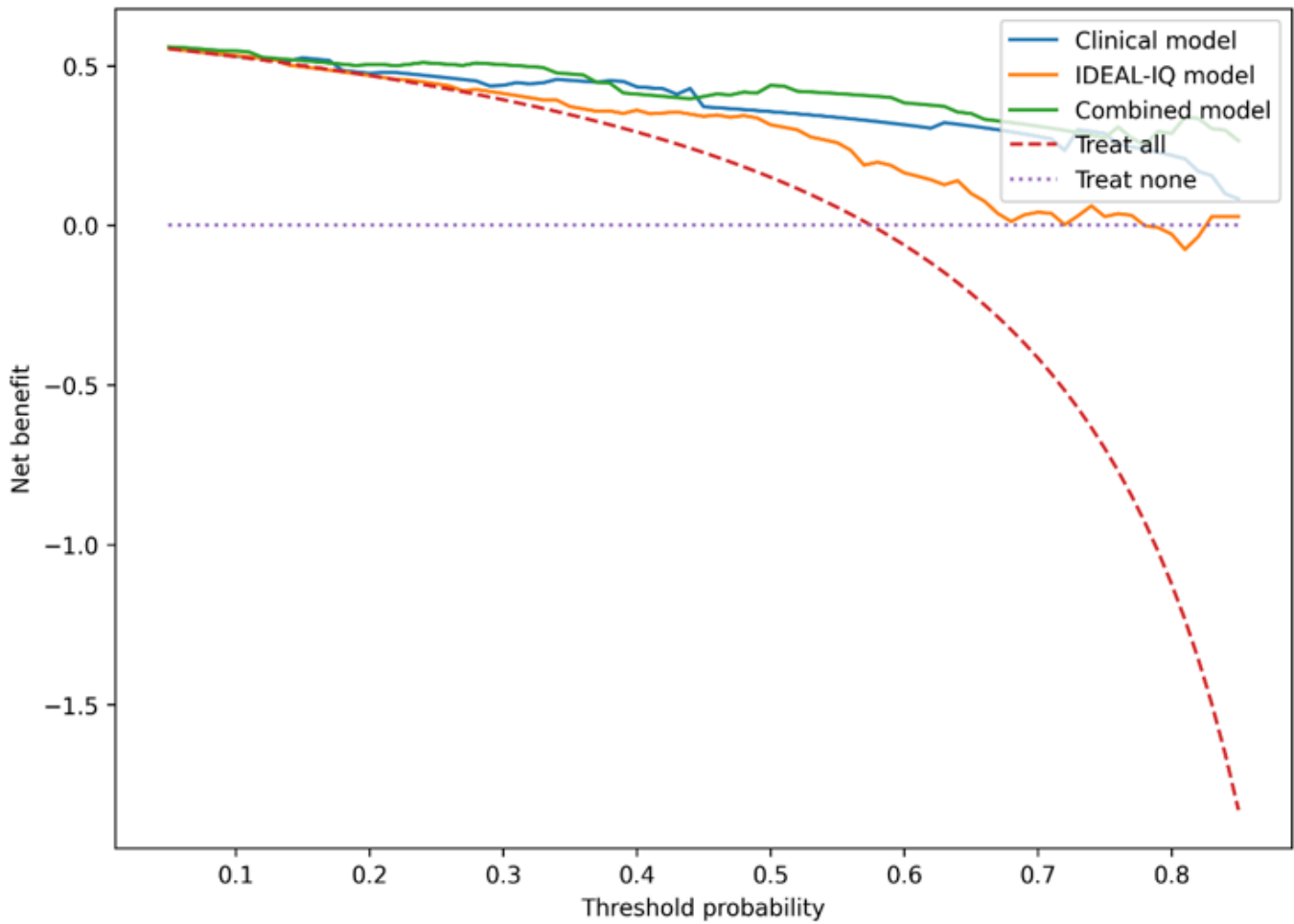


Figure 5

Decision-curve analysis of the clinical, dFF-only, and combined models. The combined model showed positive estimated net benefit over the treat-all and treat-none strategies across a range of threshold probabilities, with only modest differences from the clinical model. These findings are exploratory and require external validation.

Supplementary Files

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