Integrated MRI-Derived, Pathologic, and Molecular Biomarkers for Prediction of Neoadjuvant Chemotherapy Response in Breast Cancer

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Abstract

Aim: To investigate the predictive value of pretreatment breast magnetic resonance imaging (MRI) findings, clinicopathological characteristics, and molecular tumor features for pathological response to neoadjuvant chemotherapy (NACT).

Method: This retrospective study included 194 patients with invasive breast cancer who underwent pretreatment breast MRI, received NACT, and subsequently underwent surgery between 2015 and 2020. Pathological response was assessed using the Miller–Payne grading system and categorized as complete/near-complete response (grades 4–5), partial response (grade 3), or limited response (grades 1–2). Quantitative and morphological MRI parameters, together with clinicopathological and molecular characteristics, were analyzed. Independent predictors of pathological response were identified using multinomial logistic regression analysis.

Results: According to the Miller–Payne classification, 80 patients (41.2%) achieved complete/near-complete response, 98 (50.5%) partial response, and 16 (8.2%) limited response. Histologic subtype, tumor grade, HER2 status, Ki-67 index, molecular subtype, ADC, BPE, tumor margins, enhancement pattern, and MSI were significantly associated with pathological response. In multivariable analysis, non-ductal histology and minimal BPE independently predicted limited versus complete/near-complete response, whereas non-luminal molecular subtype, minimal BPE, and MSI ≥429 independently predicted limited versus partial response. Lower ADC independently distinguished partial from complete/near-complete response. However, substantial overlap in biological and imaging features remained across response groups.

Conclusion: Pretreatment MRI biomarkers may provide complementary information for predicting NACT response when interpreted with clinicopathologic and molecular features. Lower ADC was not an independent predictor of limited response. The occurrence of similar biological and imaging features in both

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ETHICAL STATEMENT: The study was approved by the Clinical Research Ethics Committee of Istanbul Training and Research Hospital (Decision No: 3, Approval Date: January 14, 2022). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

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highly responsive and limited-response tumors highlights substantial treatment-response heterogeneity and supports an integrated multiparametric assessment rather than reliance on any single biomarker.

Keywords: Breast cancer, neoadjuvant chemotherapy, breast MRI, imaging biomarkers, pathological treatment response.

Meme Kanserinde Neoadjuvan Kemoterapi Yanıtının Öngörülmesinde MRG Tabanlı, Patolojik ve Moleküler Biyobelirteçler

Öz

Amaç: Bu çalışmanın amacı, meme kanserli hastalarda neoadjuvan kemoterapiye (NAKT) patolojik yanıtın öngörülmesinde tedavi öncesi meme manyetik rezonans görüntüleme (MRG) bulguları ile klinikopatolojik ve moleküler tümör özelliklerinin prediktif değerini araştırmaktır.

Yöntem: Bu retrospektif çalışmaya, 2015–2020 yılları arasında tedavi öncesi meme MRG incelemesi yapılan, NAKT uygulanan ve ardından cerrahi tedavi gerçekleştirilen 194 invaziv meme kanseri hastası dahil edildi. Patolojik yanıt Miller–Payne derecelendirme sistemine göre değerlendirildi ve tam/tama yakın yanıt (derece 4–5), parsiyel yanıt (derece 3) ve sınırlı yanıt (derece 1–2) olarak sınıflandırıldı. Kantitatif ve morfolojik MRG parametreleri ile klinikopatolojik ve moleküler özellikler analiz edildi. Patolojik yanıtın bağımsız belirleyicileri multinomiyal lojistik regresyon analizi ile değerlendirildi.

Bulgular: Miller–Payne sınıflamasına göre hastaların 80'i (%41,2) tam/tama yakın, 98'i (%50,5) parsiyel ve 16'sı (%8,2) sınırlı yanıt gösterdi. Histolojik alt tip, tümör derecesi, HER2 durumu, Ki-67 indeksi, moleküler alt tip, ADC, BPE, tümör kenar özellikleri, kontrastlanma paterni ve MSI patolojik yanıt ile anlamlı ilişkiliydi. Çok değişkenli analizde non-duktal histoloji ve minimal BPE, tam/tama yakın yanıta göre sınırlı yanıtı; non-luminal moleküler alt tip, minimal BPE ve MSI ≥429 ise parsiyel yanıta göre sınırlı yanıtı bağımsız olarak öngördü. Düşük ADC değerleri parsiyel yanıtı tam/tama yakın yanıttan bağımsız olarak ayırt etti. Bununla birlikte, yanıt grupları arasında biyolojik ve görüntüleme özellikleri açısından belirgin örtüşme gözlendi.

Sonuç: Tedavi öncesi MRG biyobelirteçleri, klinikopatolojik ve moleküler özelliklerle birlikte değerlendirildiğinde NAKT yanıtının öngörülmesine tamamlayıcı bilgi sağlayabilir. Düşük ADC sınırlı yanıtın bağımsız belirleyicisi değildir. Aynı biyolojik ve görüntüleme özelliklerinin hem yüksek hem de sınırlı yanıt gösteren tümörlerde bulunabilmesi, tedavi yanıtındaki belirgin heterojenliği ortaya koymakta ve tek bir belirteç yerine bütünleşik, multiparametrik değerlendirmeyi desteklemektedir.

Anahtar Sözcükler: Meme kanseri, neoadjuvan kemoterapi, meme MRG, görüntüleme biyobelirteçleri, patolojik tedavi yanıtı.

Introduction

Neoadjuvant chemotherapy (NACT) has become an integral component of modern breast cancer management, particularly for patients with HER2-positive and triple-negative breast cancer. In addition to increasing the feasibility of breast-conserving surgery, NACT facilitates axillary de-escalation strategies and offers a unique opportunity to evaluate tumor sensitivity to systemic therapy through post-treatment pathologic assessment. Achieving a pathologic complete response (pCR) is consistently associated with favorable long-term outcomes, whereas residual disease is linked to an increased risk of recurrence and poorer survival[1,2]. However, residual disease represents a biologically heterogeneous entity, and prognosis varies according to the extent of

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residual tumor burden and intrinsic tumor characteristics[3,4]. Consequently, identifying pretreatment factors predictive of treatment response remains an important clinical objective.

Treatment response to NACT is determined by a complex interplay of clinicopathologic and molecular characteristics, including histologic subtype, tumor grade, hormone receptor status, HER2 expression, Ki-67 proliferation index, and molecular subtype[3,4]. Breast magnetic resonance imaging (MRI) provides complementary information by characterizing both tumor morphology and functional features of the tumor microenvironment. Conventional morphologic findings, apparent diffusion coefficient (ADC) values, and dynamic contrast-enhanced MRI parameters have all been investigated as potential imaging biomarkers for predicting treatment response[5,6].

More recently, radiomics and deep learning–based models have demonstrated promising predictive performance. Nevertheless, their routine clinical implementation remains limited because of concerns regarding interpretability, reproducibility, external validation, and real-world applicability[7-10]. In contrast, MRI-derived imaging biomarkers, together with routinely available pathologic and molecular characteristics, can be readily incorporated into multidisciplinary decision-making without requiring additional software, complex post-processing, or specialized imaging protocols.

We investigated the predictive value of pretreatment MRI-derived imaging biomarkers, together with clinicopathologic and molecular characteristics, for pathologic response following NACT in patients with breast cancer.

Material and Methods

Patient Selection and Inclusion Criteria

A retrospective review of our institutional database was conducted to screen individuals with histologically validated invasive breast carcinoma who were managed via a multidisciplinary approach and received NACT between January 2015 and December 2020. Eligibility criteria required the completion of neoadjuvant therapy at our center, the availability of baseline breast MRI scans, subsequent definitive surgical intervention, and accessible histopathologic evaluation of surgical specimens to determine treatment response. Patients were excluded if clinical data were incomplete, pretreatment breast MRI was unavailable, surgery had been performed outside our institution, or pre- or post-treatment pathologic records were missing. After these exclusions, 194 patients remained for the final analysis.

Clinicopathologic Variables

Clinical and histopathologic data were retrieved from the hospital information system (HIS). Variables of interest included histologic subtype, tumor grade, ER status, PR status, HER2 status, Ki-67 proliferation index, and molecular subtype. According to immunohistochemical findings, tumors were categorized as luminal A, luminal

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B/HER2-negative, luminal B/HER2-positive, HER2-enriched, or triple-negative breast cancer.

MRI Acquisition and Analysis

All patients underwent pretreatment breast MRI on a 1.5-T SIGNA Explorer system (GE Healthcare, Milwaukee, WI, USA) using a dedicated bilateral breast coil. The protocol included T2-weighted imaging, diffusion-weighted imaging with b values of 0 and 800 s/mm², and three-dimensional fat-suppressed T1-weighted dynamic contrast-enhanced MRI. ADC maps were automatically generated from images acquired at both b values. A gadolinium-based contrast agent (0.1 mmol/kg) was administered at 2 mL/s, followed by a 20-mL saline flush. Five postcontrast phases were acquired at 60-second intervals.

MRI examinations were retrospectively reviewed for morphologic and quantitative imaging biomarkers. Morphologic variables included lesion morphology, tumor margins, background parenchymal enhancement (BPE), enhancement distribution pattern, ipsilateral breast vascularity, and axillary nodal involvement.

Quantitative parameters included the ADC, time to peak enhancement (TTP), maximum signal increase (MSI), and baseline MRI tumor size. ADC was measured using manually placed circular regions of interest (30–50 mm²) positioned over the lowest-ADC region within the solid tumor while avoiding necrotic, cystic, and hemorrhagic areas. The lowest value (ADCmin) was used for analysis.

Dynamic contrast-enhanced (DCE) MRI analyses were performed on a GE Advantage Workstation using the manufacturer's standard software. MSI represented the maximum percentage increase in signal intensity relative to baseline, whereas TTP represented the interval between contrast administration and peak enhancement.

Pathologic Response Assessment

Following completion of NACT, patients underwent definitive breast surgery. Surgical specimens were evaluated by dedicated breast pathologists, and treatment response was graded according to the Miller–Payne grading system. Responses were categorized as complete/near-complete (grades 4–5), partial (grade 3), or limited (grades 1–2). In the present study, Miller–Payne grades 1–2 were classified as limited response, reflecting only minimal reduction in tumor cellularity following NACT. This response classification served as the primary study outcome.

Ethical Statement

The study protocol was approved by the Clinical Research Ethics Committee of Istanbul Training and Research Hospital, Türkiye (Decision No: 3, Date: January 14, 2022).

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Statistical Analysis

Continuous variables were assessed for normality and summarized as mean ± standard deviation (SD). Comparisons among the three response groups were performed using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables, whereas categorical variables were analyzed using the chi-square test. ROC curve analysis was used to determine optimal cutoff values for quantitative MRI biomarkers. Variables showing significant associations in univariable analyses were entered into a multinomial logistic regression model to identify independent predictors of treatment response. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics and Pathologic Response

The final cohort included 194 patients. Of these, 80 (41.2%) achieved a complete or near-complete pathologic response, 98 (50.5%) had a partial response, and 16 (8.2%) demonstrated limited response after NACT. Age, family history of breast cancer, lymphovascular invasion, tumor necrosis, progesterone receptor status, and baseline tumor size were comparable across the three response groups (all $p>0.05$). Conversely, histologic subtype, tumor grade, HER2 expression, Ki-67 proliferation index, and molecular subtype differed significantly according to treatment response (Table 1).

Invasive ductal histology and HER2-positive tumors were observed more frequently in patients who achieved a complete or near-complete response, whereas both features were less common in patients with partial or limited response. Tumor grade also differed significantly among the three response categories. Molecular subtype distribution varied significantly ($p<0.001$), with HER2-positive molecular subtypes overrepresented among complete or near-complete responders, whereas triple-negative tumors accounted for more than half of the limited-response group (56.3%). When classified according to biologic phenotype, non-luminal tumors were significantly more common in patients with limited response than in those with complete or near-complete or partial response (62.5%, 33.8%, and 26.5%, respectively; $p=0.016$).

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Table 1. Clinicopathologic characteristics according to pathologic response category. complete/near-complete response, Miller–Payne grades 4–5; partial response, Miller–Payne grade 3; limited response, Miller–Payne grades 1–2.

Characteristic	**Complete/ Near-complete (n=80)**	**Partial (n=98)**	**Limited (n=16)**	**p**
Invasive ductal carcinoma, n (%)	69 (86.3)	71 (72.4)	9 (56.3)	0.012
Grade III, n (%)	45 (60.0)	35 (36.1)	11 (68.8)	0.002
HER2-positive, n (%)	37 (46.3)	21 (21.4)	4 (25.0)	0.002
Ki-67 ≥35%, n (%)	56 (70.9)	51 (52.0)	14 (87.5)	0.004
Non-luminal molecular subtype, n (%)	27 (33.8)	26 (26.5)	10 (62.5)	0.016

Abbreviations: HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Note: Non-luminal molecular subtype comprised HER2-enriched and TNBC tumors. HER2-positive refers to HER2 receptor status. Percentages were calculated using available data.

MRI Findings and Quantitative Imaging Biomarkers

Overall lesion morphology, lesion location, enhancement symmetry, time-to-peak enhancement, kinetic curve type, baseline tumor size, and extensive nodal involvement were not associated with treatment response (all $p>0.05$).

Among qualitative MRI features, circumscribed or lobulated margins were more frequent in patients with limited response than in complete/near-complete or partial responders (62.5% vs. 27.5% and 32.7%, $p=0.025$). Minimal BPE was also more common in patients with limited response (37.5% vs. 11.3% and 10.2%, $p=0.009$).

Quantitative MRI biomarkers also differed across response groups. Mean ADC values were highest in complete/near-complete responders ($0.92\pm0.16\times10^{-3}$ mm²/s), intermediate in partial responders ($0.87\pm0.13\times10^{-3}$ mm²/s), and lowest in patients with limited response ($0.79\pm0.24\times10^{-3}$ mm²/s; $p=0.002$). ADC values $>0.93\times10^{-3}$ mm²/s were more common among complete/near-complete responders than among partial or limited responders (47.5% vs. 29.6% and 31.3%, $p=0.043$). Peripheral enhancement was observed more frequently in patients with limited response (53.3% vs. 30.0% and 22.7%, $p=0.043$). MSI was highest in patients with limited response (405.6±212.9), followed by complete/near-complete (303.9±166.1) and partial responders (288.4±130.5; $p=0.017$), whereas MSI ≥429 was associated with limited response (p=0.040).

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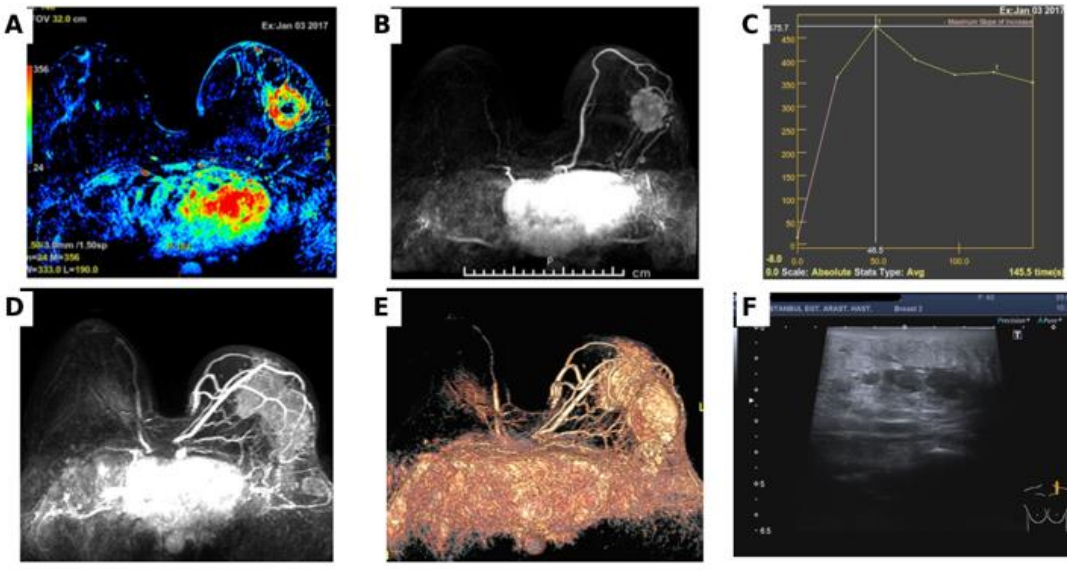
Figure 1. Representative case of poor response to NACT.



A 40-year-old woman with cT2N1 grade 3 TNBC of the left breast. Pretreatment MRI demonstrates marked enhancement on the maximum signal increase map (A), an enhancing breast mass on MIP (B), and rapid early enhancement on kinetic analysis (C). Despite NACT, follow-up MRI (D, E) and US (F) demonstrate marked local tumor progression with associated breast edema and axillary lymphadenopathy, consistent with progressive disease, which was confirmed by surgical pathology.

Abbreviations: TNBC, triple-negative breast cancer; NACT, neoadjuvant chemotherapy; MSI, maximum signal increase; MIP, maximum-intensity projection imaging; US, ultrasonography.

Table 2. MRI Findings and Quantitative Imaging Biomarkers.

Variable	Complete/ Near-complete	Partial	Limited Response	p
Circumscribed or lobulated margin, n (%)	22 (27.5)	32 (32.7)	10 (62.5)	0.025
Minimal BPE, n (%)	9 (11.3)	10 (10.2)	6 (37.5)	0.009
ADC, mean ± SD (×10⁻³ mm²/s)	0.92±0.16	0.87 ± 0.13	0.79±0.24	0.002
ADC >0.93 ×10⁻³ mm²/s, n (%)	38 (47.5)	29 (29.6)	5 (31.3)	0.043
Peripheral enhancement, n (%)	24 (30.0)	22 (22.7)	8 (53.3)	0.043
MSI, mean ± SD	303.9±166.1	288.4±130.5	405.6±212.9	0.017
MSI ≥429, n (%)	16 (20.0)	16 (16.3)	7 (43.8)	0.040

Abbreviations: ADC, apparent diffusion coefficient; BPE, background parenchymal enhancement; MSI, maximum signal increase. Percentages were calculated using available data.

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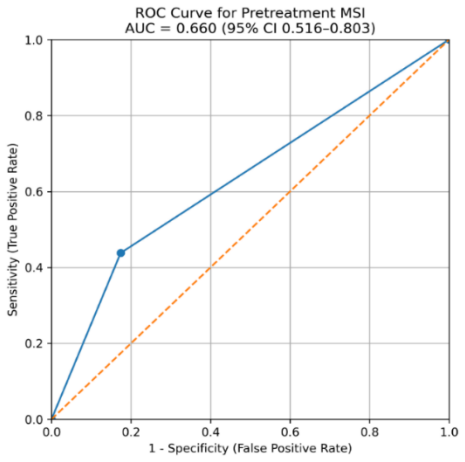
ROC Analysis

ROC analysis demonstrated that pretreatment ADC values were significantly associated with complete/near-complete pathologic response. The AUC for ADC was 0.613 (95% CI: 0.532–0.693; p = 0.008). The optimal cutoff value was 0.93 × 10^{-3} mm^2/s, yielding a sensitivity of 47.5% and a specificity of 70.2% for identifying complete/near-complete response.

For prediction of limited response, MSI also demonstrated significant discriminatory performance. The AUC was 0.660 (95% CI: 0.516–0.803; p=0.034). The optimal MSI cutoff value was 429, corresponding to a sensitivity of 43.8% and a specificity of 82.6%.

Figure 2. ROC curve of pretreatment MSI for prediction of limited response following NACT.



The AUC was 0.660 (95% CI: 0.516–0.803; p=0.034). The optimal cutoff value was 429, corresponding to a sensitivity of 43.8% and specificity of 82.6%.

Abbreviations: ROC, receiver operating characteristic; MSI, maximum signal increase; AUC, area under the curve; CI, confidence interval.

Multivariable Analysis

Using complete/near-complete response as the reference category, non-ductal histology (OR=2.30, 95% CI: 1.03–5.13; p=0.041) and low ADC values (≤0.93×10^{-3} mm^2/s; O=2.06, 95% CI: 1.08–3.93; p=0.028) independently predicted partial response. When limited response was compared with complete/near-complete response, non-ductal histology (OR=3.99, 95% CI: 1.01–15.87; p=0.049) and minimal background parenchymal enhancement (BPE) (OR=4.92, 95% CI: 1.23–19.71; p=0.024) independently predicted limited response. Finally, with partial response as the reference category, non-luminal molecular subtype (OR=4.54, 95% CI: 1.13–18.18; p=0.033), minimal BPE (OR=5.69, 95% CI: 1.44–22.47; p=0.013), and MSI ≥429 (OR=4.32, 95% CI: 1.15–16.19; p=0.030) independently predicted limited response.

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Overall, biological tumor characteristics and MRI-derived biomarkers provided complementary information for treatment-response stratification. The multinomial logistic regression results are presented in Table 3 and graphically summarized in Figure 3.

Table 3. Independent predictors of pathologic response identified by multinomial logistic regression.

Comparison / Predictor	**OR (95% CI)**	**P**
Partial vs Complete/near-complete		
Non-ductal histology	2.30 (1.03–5.13)	0.041
ADC ≤0.93 ×10⁻³ mm²/s	2.06 (1.08–3.93)	0.028
Limited vs Complete/near-complete		
Non-ductal histology	3.99 (1.01–15.87)	0.049
Minimal BPE	4.92 (1.23–19.71)	0.024
Limited vs Partial		
Non-luminal subtype	4.54 (1.13–18.18)	0.033
Minimal BPE	5.69 (1.44–22.47)	0.013
MSI ≥429	4.32 (1.15–16.19)	0.030

Abbreviations: OR, odds ratio; CI, confidence interval; ADC, apparent diffusion coefficient; BPE, background parenchymal enhancement; MSI, maximum signal increase.

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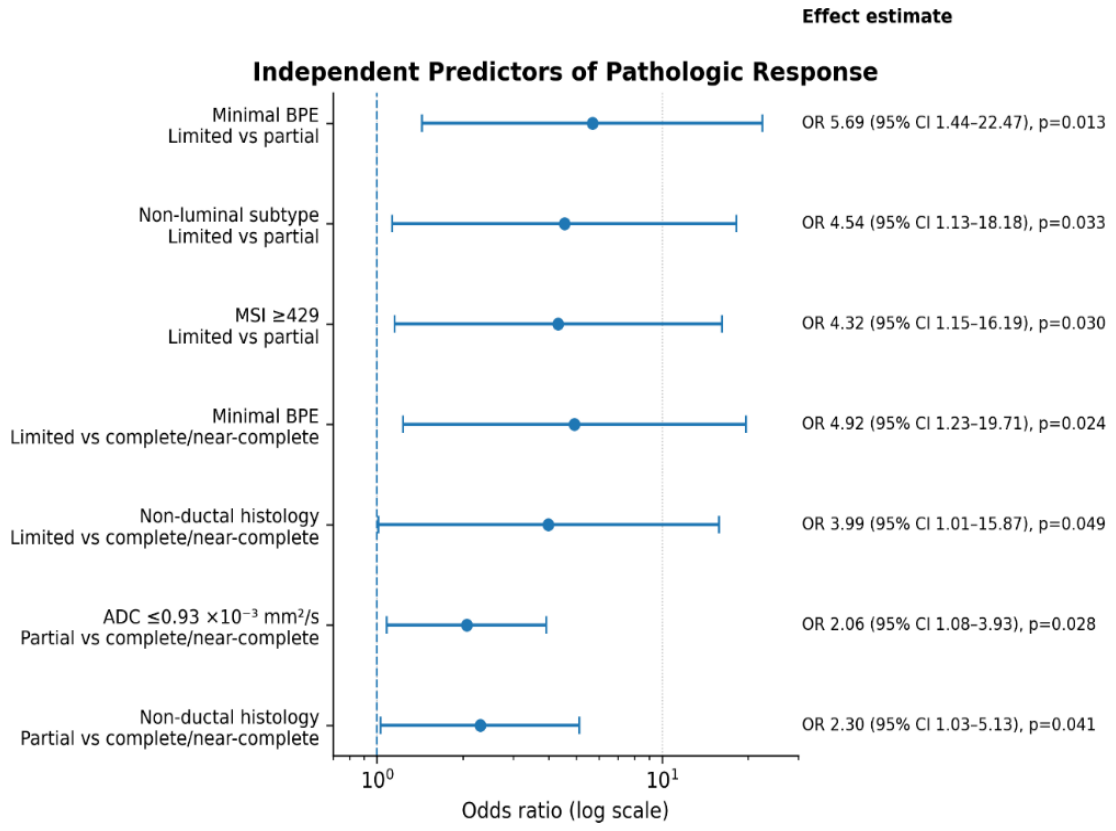
Figure 3. Independent predictors of pathologic response after neoadjuvant chemotherapy.



Forest plot showing ORs and 95% CIs derived from multinomial logistic regression analysis. Limited response corresponds to Miller–Payne grades 1–2, representing tumors with minimal reduction in tumor cellularity following NACT.

Abbreviations: OR, odds ratio; CI, confidence interval; ADC, apparent diffusion coefficient; BPE, background parenchymal enhancement; MSI, maximum signal increase.

Discussion

NACT is a cornerstone of treatment for biologically aggressive breast cancer because it facilitates surgical downstaging while providing an in vivo assessment of treatment sensitivity. Although established clinicopathologic factors remain the principal determinants of response, accurate pretreatment identification of patients at risk for poor response continues to represent an important clinical challenge. In the present cohort, histologic subtype, tumor grade, HER2 status, Ki-67 proliferation index, and molecular subtype were strongly associated with pathologic response, confirming the central role of intrinsic tumor biology. Importantly, MRI-derived biomarkers, particularly ADC, BPE, and MSI, provided complementary information beyond these

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established factors, suggesting that treatment response reflects both intrinsic tumor biology and imaging-visible characteristics of the tumor microenvironment[4-6,11].

Despite these established biologic determinants, substantial variability persisted within individual molecular subgroups, indicating that biologic classification alone does not fully explain treatment sensitivity[4,12–14]. Patients with apparently similar clinicopathologic profiles frequently exhibited markedly different treatment outcomes, suggesting that MRI-derived biomarkers reflecting the tumor microenvironment provide complementary information for pretreatment response prediction. Consistent with this observation, patients with limited response in our cohort represented a biologically distinct subgroup characterized not only by adverse clinicopathologic features but also by distinctive MRI findings.

Luminal tumors exhibited lower rates of complete or near-complete response than HER2-positive tumors, consistent with their lower chemosensitivity. However, they rarely demonstrated marked treatment resistance, indicating that failure to achieve pCR should not automatically be interpreted as treatment failure in hormone receptor-positive disease. Conversely, despite generally favorable response rates to NACT, TNBC accounted for more than half of the limited-response tumors in our cohort, underscoring the biologic heterogeneity of this subtype. Previous molecular classifications similarly demonstrated substantial variation in chemosensitivity across TNBC subtypes. Lehmann et al. reported the highest pCR rates in basal-like 1 tumors, whereas luminal androgen receptor and mesenchymal subtypes more frequently exhibited residual disease. Similarly, Bianchini et al. emphasized the clinical heterogeneity of TNBC and its implications for treatment response. This heterogeneity was also reflected in our imaging findings, in which minimal BPE, lower ADC values, and elevated MSI were more common among patients with limited response[4,12–14].

ADC showed a graded association with treatment response, with the highest mean values observed in complete/near-complete responders and the lowest values in patients with limited response. However, dichotomized low ADC independently distinguished partial from complete/near-complete response but did not remain an independent predictor in comparisons involving limited response. These findings suggest that ADC reflects tumor cellularity and treatment sensitivity but may have limited specificity as an isolated marker of treatment resistance. Its interpretation may also be influenced by underlying histopathologic heterogeneity, particularly in tumors with mixed or metaplastic components[15,16].

Among the imaging biomarkers evaluated, BPE was one of the strongest predictors of limited response. Increasing evidence suggests that BPE reflects not only hormonal status but also characteristics of the breast microenvironment[17–19]. A recent systematic review by Li and Yan summarized the growing evidence linking BPE to response following NACT, although study findings remain heterogeneous[17]. Similarly, Preibsch et al. demonstrated that changes in BPE during treatment correlate with response, whereas Onishi et al. reported poorer outcomes in patients without BPE suppression[18,19]. Consistent with these observations, pretreatment minimal BPE remained an

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independent predictor of limited response in our cohort. These findings suggest that minimal BPE is not a deterministic marker of treatment resistance but rather a clinically relevant pretreatment imaging biomarker that identifies patients at increased risk of limited response.

DCE MRI parameters provided additional information regarding treatment sensitivity. MSI remained independently associated with limited rather than partial response after adjustment for clinicopathologic and molecular variables. As a measure of enhancement intensity, elevated MSI may reflect increased angiogenic activity, vascular permeability, and tumor perfusion. Together, ADC and MSI provide complementary information on the cellular and vascular components of tumor biology. Considerable overlap between response groups remained despite the associations observed. Although non-luminal molecular subtypes and non-ductal histology were more common among patients with limited response, many patients with these characteristics still achieved favorable treatment outcomes, underscoring the biologic heterogeneity within molecular classification of breast cancer[4,12-14]. Rather than serving as deterministic markers of treatment resistance, these clinicopathologic and imaging features should be viewed as risk indicators that identify patients more likely to exhibit limited response and who may benefit from closer monitoring during NACT.

Morphologic MRI features also differed according to treatment response. Circumscribed or lobulated margins and peripheral enhancement are frequently encountered in TNBCs with favorable responses to neoadjuvant chemotherapy; however, similar features were also observed in a subset of non-luminal tumors with limited response. These findings indicate that MRI morphology reflects underlying tumor biology rather than treatment sensitivity alone. Although morphologic features were not independent predictors in multivariable analysis, they may provide valuable complementary information when interpreted alongside quantitative MRI biomarkers and molecular characteristics and could therefore contribute to a multiparametric prediction model. Consistent with our findings, Goorts et al. demonstrated that MRI response patterns correlate with pathologic outcome following NACT, supporting the complementary role of imaging in treatment response assessment[20].

The observation that relatively well-defined tumor margins were also encountered among some tumors with limited response may initially appear counterintuitive. However, certain histologic subtypes, particularly metaplastic breast carcinomas, are known to exhibit deceptively circumscribed or lobulated imaging appearances despite their aggressive biologic behavior. McCart Reed et al. highlighted the molecular and prognostic aggressiveness of metaplastic breast cancer, while Yoon et al. described its tendency to present with relatively circumscribed imaging morphology[15,16]. Therefore, morphologic MRI findings should not be interpreted as direct indicators of treatment resistance but rather as imaging manifestations of the biologic heterogeneity that exists across breast cancer subtypes.

A major strength of the present study is its clinical applicability. All imaging biomarkers evaluated—including tumor morphology, ADC, BPE, and MSI—were derived from

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routine breast MRI examinations using standard vendor-provided post-processing tools and did not require dedicated radiomics platforms or additional specialized software. Likewise, the accompanying biologic variables are already available from standard pathologic assessment. Because breast MRI is an established component of neoadjuvant treatment planning, integrating these routinely available imaging and biologic data into response prediction could be implemented without altering current clinical workflows[2,5,17].

Although patients with limited response represented only a small proportion of the cohort (8.2%), their clinical importance is disproportionately high. Previous studies have demonstrated that residual disease following NACT is associated with substantially different long-term outcomes according to residual disease burden and breast cancer subtype[4,14]. Failure to recognize poorly responding tumors before or early during neoadjuvant treatment may result in ineffective treatment exposure, delays in definitive local therapy, and missed opportunities for timely treatment modification.[11] Therefore, the ability to identify patients at increased risk for limited response before treatment initiation may have important clinical implications. Importantly, the imaging and biologic features identified in our study should not be interpreted as deterministic markers of treatment resistance. Rather, they may help define a subgroup in which treatment-resistant disease is encountered more frequently, consistent with the well-recognized heterogeneity of treatment response observed within individual breast cancer subtypes[4,14].

This study has several limitations. First, its retrospective single-center design may have introduced selection bias. Second, the limited-response group was small (n = 16), reducing statistical power and resulting in wide 95% confidence intervals for several multivariable estimates; these findings should therefore be interpreted cautiously. Third, MSI measurements were derived using vendor-specific post-processing software, which may limit the generalizability of the proposed threshold across different MRI platforms. Fourth, although several MRI-derived biomarkers emerged as independent predictors of treatment response, the study was not designed to develop or externally validate a predictive model. In addition, residual cancer burden (RCB) was not routinely assessed during the study period; therefore, treatment response was evaluated using the Miller–Payne grading system. External validation in independent cohorts will be necessary to confirm the reproducibility and generalizability of these findings.

Conclusion

Pretreatment breast MRI findings may provide complementary information for predicting response to NACT when interpreted together with clinicopathologic and molecular features. Non-ductal histology, non-luminal molecular subtype, minimal BPE, and elevated MSI were associated with limited response, whereas lower ADC independently distinguished partial from complete/near-complete response but was not an independent predictor of limited response. Importantly, similar biological and imaging features were observed in both highly responsive and limited-response tumors, highlighting substantial treatment-response heterogeneity within the same phenotypic

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profiles. These findings suggest that such biomarkers should not be interpreted as isolated markers of resistance, but rather as complementary indicators supporting integrated pretreatment risk stratification.

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