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Comparison of Microsatellite Instability (MSI) and Microsatellite Stable (MSS) Invasive Breast Carcinoma Cases In Terms Of Neoadjuvant Chemotherapy Response, ER/PR Status, CerbB2, and Ki-67

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ABSTRACT

Introduction: Microsatellite instability (MSI) is a well-established biomarker in certain malignancies; however, its prognostic and predictive role in breast cancer remains unclear. This study aimed to compare invasive breast carcinoma cases with MSI and those with microsatellite stability (MSS) regarding response to neoadjuvant chemotherapy (NACT), estrogen and progesterone receptor status, c-erbB-2 (CerbB2) expression, Ki-67 proliferation index, and clinicopathological features, using immunohistochemical (IHC) assessment of mismatch repair (MMR) protein expression.

Methods: Eighty-seven patients with invasive breast carcinoma who had received NACT were retrospectively analyzed. MMR protein expression was evaluated by IHC for MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and postmeiotic segregation increased 2 (PMS2). Clinicopathological and IHC variables, including Miller–Payne classification, Pinder lymph node response, hormone receptor status, Ki-67, and CerbB2 expression, were compared between MSI and MSS groups. Survival analyses were performed using the Kaplan–Meier method.

Results: MSI was detected in 8% of patients (7/87). Loss of nuclear expression was observed in MLH1/PMS2 (3 cases, 42%), MSH2/MSH6 (2 cases, 29%), and isolated PMS2 (2 cases, 29%). No significant differences were found between the MSI and MSS groups in terms of chemotherapy response, clinicopathological variables, or overall survival and disease-free survival ($p>0.05$).

Conclusion: MSI was identified in 8% of invasive breast carcinoma cases but showed no significant association with NACT response, clinicopathological features, or survival outcomes. Its prognostic and predictive role in breast cancer remains uncertain and warrants confirmation in larger prospective studies.

Keywords: Mismatch repair, microsatellite instability, neoadjuvant chemotherapy, breast carcinoma, hormone receptors, Ki-67, CerbB2

Introduction

Breast carcinoma represents the most prevalent malignancy among women. According to SEER reports, 316,950 new cases of breast carcinoma were diagnosed in 2025; the majority were locally advanced at presentation (1). Neoadjuvant chemotherapy (NACT) is the current standard therapeutic approach for locally advanced breast cancer (2). However, this disease entity is highly heterogeneous with respect to both treatment response and survival outcomes (3).

Deficiencies in mismatch repair (MMR) proteins in breast cancer highlight their critical role in DNA repair mechanisms and may facilitate the acquisition of resistance to chemotherapeutic agents by tumor cells. Consequently, MMR deficiency is considered a potential contributor to breast cancer progression (4).

Microsatellites are short repetitive DNA sequences, typically comprising repeat units of 1–6 base pairs, such as [A]n or [CA]n. The MMR system involves key proteins, including MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and postmeiotic segregation

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increased 2 (PMS2) (5). Microsatellite instability (MSI), defined as random insertions or deletions resulting in alterations of microsatellite length, has been documented in a variety of tumor types (6).

Defects in the DNA MMR system are closely linked to the development of MSI; however, these entities are conceptually and diagnostically distinct. In normal cells, microsatellite sequences are maintained with high fidelity, whereas impaired MMR function allows replication-associated insertion–deletion errors to persist, resulting in alterations in microsatellite length. Accordingly, MSI represents a molecular consequence of defective MMR activity, while immunohistochemical (IHC) evaluation of MMR protein expression and assessment of MSI status reflect related but non-equivalent biological and diagnostic approaches (5).

The identification of MSI in multiple classes of malignancies has contributed to the broader adoption of immunotherapeutic strategies, which are presumed to be particularly effective against tumors harboring a high mutational burden and/or neoantigen load. DNA sensing mechanisms in cancer cells are essential for antitumor immune responses associated with *MMR* gene status, thereby offering novel avenues and biomarkers for immunotherapy (7).

MMR proteins are widely expressed molecules that play fundamental roles in diverse cellular processes, most notably in preserving genomic stability by correcting replication errors through post-replicative repair mechanisms. MMR deficiency has been associated with tumorigenesis and disease progression. This study aimed to investigate the relationship between MSI status and response to NACT, estrogen receptor (ER) and progesterone receptor (PR) status, c-erbB-2 (CerbB2) status, and Ki-67 expression in invasive breast carcinoma.

Methods

Definition of the Study Group

Ninety-five cases diagnosed with invasive breast carcinoma by tru-cut breast biopsy and who subsequently received neoadjuvant therapy and underwent breast resection were included in the study. Approval for the study was obtained from the Non-Interventional Scientific Research Ethics Committee of İstanbul Atlas University (approval number: 08/06, date: 29.09.2025). Eight cases were excluded because clinical data or access to pathology slides and paraffin blocks in the pathology laboratory were unavailable. Patient age and survival information were retrieved from hospital electronic medical records, while data on tumor size, tumor localization, and axillary lymph node status were obtained from radiological imaging and pathology reports.

Histomorphologic Evaluation

In the 87 cases in our study group, hematoxylin and eosin-stained slides prepared from tru-cut biopsy specimens obtained prior to NACT and from breast resection specimens following NACT were reviewed by a single pathologist. The response of the tumor to neoadjuvant therapy in the breast resection specimens was evaluated according to the Miller and Payne classification (2003) (8) and categorized into one of five grades. According to the Miller and Payne classification, Grade 1 (no response/minimal response) is defined as no reduction in tumor cells following chemotherapy, or a reduction of less than 30%. Grade 2 (mild response): a reduction of 30–90% in tumor cells, but with readily identifiable residual tumor cells. Grade 3 (moderate response): More than 90% reduction in tumor cells, with a small number of viable cells remaining. Grade 4 (good response): Only small clusters of tumor cells or single cells remain. Grade 5 (complete response): No residual invasive tumor cells (only an *in situ* ductal component may remain) (8).

The axillary lymph node response to neoadjuvant therapy was evaluated according to the Pinder classification (2007) (9) and assigned to one of four categories (10). According to the Pinder classification: Pinder 1: No metastatic tumor and no therapeutic response in lymph nodes; Pinder 2: No metastatic tumor with therapeutic response in lymph nodes (e.g., fibrosis); Pinder 3: Metastatic tumor present with therapeutic response in lymph nodes; Pinder 4: Metastatic tumor present without therapeutic response in lymph nodes.

The histological type of the tumors in the tru-cut biopsy specimens was assessed according to the 2019 World Health Organization criteria. Histological grade and nuclear grade were determined using the Modified Scarff-Bloom-Richardson/Nottingham grading system (1991) (11). During histomorphological evaluation, carcinoma *in situ* and necrosis were recorded in the tru-cut biopsy specimens.

The stromal lymphocytic response around the tumor in tru-cut biopsy specimens was evaluated according to the recommendations of the International TILs Working Group (2014) (12). Based on these recommendations, lymphocytic response was graded as follows: Grade 1: <10%; Grade 2: ≥10%; Grade 3: ≥40%.

Immunohistochemical Evaluation

IHC analysis was performed for the following markers: ER (Scyek, Rabbit, class: IgG1-kappa, clone: ERa078, dilution: 1:100); PR (Scyek, Human, class: IgG1-kappa, clone: PGR-1A6, dilution: 1:100); Ki67 (BioGenex, Mouse, class: IgG1-kappa, clone: BGX-Ki67, dilution: 1:100); CerbB2 (Thermo, Mouse, class: IgG1, clone: e2-4001 + 3B5, dilution: 1:400); MLH1 (Ventana, Mouse, clone: M1, ready-to-use); MSH2 (Ventana, Mouse, clone: G219-1129, ready-to-use); MSH6 (Ventana, Mouse, clone: SP93, ready-to-use); and PMS2 (Ventana, Mouse, clone: A16-4, ready-to-use). The evaluation of ER and PR staining was conducted in accordance with the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (10), with positivity defined as nuclear staining in ≥1% of invasive tumor cells. CerbB2 expression was assessed according to the 2018 ASCO/CAP guidelines and scored 0 (negative), 1+ (negative), 2+ (equivocal), or 3+ (positive) (13).

The Ki67 proliferation index was assessed following the international recommendations established by the Breast Cancer Study Group in 2011. Three high-power fields (× 40 magnification) from the invasive tumor area were selected, and the mean nuclear labeling index was calculated. In heterogeneous tumors, one of the three fields was designated as a hot spot, and the mean was calculated accordingly (14). Values ≥15% were considered high, and values were considered low.

MSI was defined as the absence of nuclear staining for at least one of the MLH1, MSH2, MSH6, or PMS2 antibodies in tumor cells, whereas microsatellite stability (MSS) was defined as focal or diffuse nuclear

staining for all four antibodies. Normal colonic mucosa, inflammatory cells, and stromal cells served as internal positive controls (4).

Statistical Analysis

The distribution of the data was assessed using the Shapiro–Wilk test. For variables not conforming to a normal distribution, comparisons between two independent groups were performed with the Mann–Whitney U test. Comparisons of categorical variables between groups were evaluated using Fisher's exact test or the chi-square test, as appropriate. Overall survival and disease-free survival by group were analyzed using the Kaplan–Meier method, and differences were assessed with the log-rank test. Descriptive statistics for continuous variables were expressed as means [standard deviations (SDs)] and medians (minimum–maximum), whereas categorical variables were presented as frequencies (percentages). In survival analysis, descriptive statistics for overall survival and disease-free survival were reported as mean (standard error). All statistical analyses were conducted using IBM SPSS Statistics version 29.0.2 with a significance level set at $p<0.05$.

Results

General Characteristics of the Findings

A total of 87 patients were included in the study. The mean age of the patients was 51.69 (10.88) years (range: 31–74). The mean overall survival was 48.39 (28.63) months (range: 2–108 months), and the mean disease-free survival was 46.98 (31.57) months (range: 0–108 months). At the last follow-up, 17 patients (19.5%) were alive, and 70 patients (80.5%) were deceased.

Histopathological evaluation of resection specimens revealed 75 cases (86.2%) of invasive ductal carcinoma, 8 cases (9.2%) of invasive lobular carcinoma, and 4 cases (4.6%) of mixed histology. Tumor localization was in the right breast in 43 patients (49.4%) and in the left breast in 44 patients (50.6%). The mean tumor size was 30.89 (15.29) mm (range: 9.5–86 mm). Fine-needle aspiration cytology of the axilla showed negative results in 14 patients (19.4%) and positive results in 58 patients (80.6%), while radiological evaluation of the axilla revealed negative findings in 10 patients (11.6%) and positive findings in 76 patients (88.4%). Radiological multifocality was detected in 25 patients (28.7%); the mean number of foci was 2.76 (SD: 1.09; range: 2–6).

Histological grading demonstrated Grade 1 in 6 patients (10.5%), Grade 2 in 35 patients (61.4%), and Grade 3 in 16 patients (28.1%). Nuclear grades were distributed as follows: Grade 1 in 5 patients (8.8%), Grade 2 in 28 patients (49.1%), and Grade 3 in 24 patients (42.1%). Lymphovascular invasion (LVI) was present in 30 patients (34.5%) and perineural invasion (PNI) was present in 17 patients (19.5%). Ductal carcinoma *in situ* was identified in 34 cases (39.1%), while lobular carcinoma *in situ* was observed in 2 cases (2.3%).

IHC evaluation revealed ER positivity in 50 patients (89.3%) and ER negativity in 6 patients (10.7%). PR was positive in 43 patients (76.8%) and negative in 13 patients (23.2%). CerbB2 expression was negative in 38 patients (66.7%) and positive in 19 patients (33.3%). The distribution of CerbB2 scores was as follows: 0 in 25 patients (43.9%), 1 in 13 patients (22.8%), 2 in 2 patients (3.5%), and 3 in 17 patients (29.8%).

According to the Miller–Payne grading system, 7 patients (8%) were Grade 1 (no or minimal response), 13 (14.9%) were Grade 2 (minimal response; 30–90% reduction in tumor cells), 23 (26.4%) were Grade 3 (moderate response; >90% reduction in tumor cells), 14 (16.1%) were Grade 4 (good response; small clusters or isolated tumor cells), and 30 (34.5%) were Grade 5 (complete response; no viable tumor cells).

Based on the Pinder classification, 28 patients (32.6%) were Grade 1 (no metastatic tumor and no treatment response in lymph nodes), 10 (11.6%) were Gade 2 (no metastatic tumor and treatment response in lymph nodes such as fibrosis), 33 (38.4%) were Grade 3 (metastatic tumor present and treatment response in lymph nodes), and 15 (17.4%) were Grade 4 (metastatic tumor present and no treatment response in lymph nodes).

The mean Ki-67 proliferation index was 28% (SD: 20%; range, 2–85%). Seven cases (8%) demonstrated MSI, whereas 80 cases (92%) were MSS. Among the MSI cases, loss of MLH1/PMS2 nuclear expression was detected in 3 patients (42%), loss of MSH2/MSH6 nuclear expression in 2 patients (29%), and isolated loss of PMS2 nuclear expression in 2 patients (29%). The results are summarized in Table 1.

Microsatellite Instability Status

The results of statistical comparisons between the MSI group (Figure 1) and the MSS group with respect to the Miller–Payne classification; the Pinder lymph node scoring system; ER, PR, Ki67, CerbB2, and CerbB2 score (each assessed in resection and biopsy specimens); molecular subtype; stromal lymphocyte percentage and grade; intratumoral lymphocytic response; overall survival; disease-free survival; recurrence or metastasis; and mortality status are presented in Table 2. As shown in Table 2, no statistically significant differences were observed between groups for these variables ($p>0.05$). The distribution of molecular subtypes according to MSI status is illustrated in Figure 2.

The results of the statistical comparisons between the MSS and MSI groups in terms of tumor size, histological subtype, age, localization, quadrant, number of foci, histological grade, nuclear grade, LVI, PNI, and *in situ* components in the resection specimens are presented in Table 3. As shown in Table 3, none of these variables demonstrated statistically significant differences between the groups ($p>0.05$).

Similarly, statistical comparisons between MSS and MSI groups in biopsy specimens with respect to histological subtype, histological grade, nuclear grade, LVI, PNI, *in situ* components, and necrosis are summarized in Table 4. No statistically significant differences were observed between the groups for these biopsy-related variables ($p>0.05$).

Kaplan–Meier analysis was performed to evaluate overall survival and disease-free survival according to MSI and MSS status (Table 5, Figure 3). As shown in the table, overall survival did not differ significantly between the MSS and MSI groups ($p=0.659$). Disease-free survival according to MSI status is presented in Table 6; similarly, no statistically significant difference was found between the MSS and MSI groups ($p=0.806$) (Figure 4).

Discussion

Breast cancer remains the leading cause of cancer-related mortality worldwide and demonstrates marked heterogeneity in its

Table 1. Demographic, clinical, and pathological characteristics of patients included in the study

Variable	Value
Demographic data	
Descriptive statistics	
Number of patients	n=87
Age (years)	51.69±10.88 (31–74)
Overall survival (months)	48.39±28.63 (2–108)
Disease-free survival (months)	46.98±31.57 (0–108)
Survival status	
Alive	17 (19.5)
Dead	70 (80.5)
Resection subtype	
IDC	75 (86.2)
Lobular	8 (9.2)
Mixed	4 (4.6)
Localization	
1	43 (49.4)
2	44 (50.6)
Pathology IIAB	
Negative	14 (19.4)
Positive	58 (80.6)
Radiological axilla	
Negative	10 (11.6)
Positive	76 (88.4)
Radiological multifocality	
Absent	62 (71.3)
Present	25 (28.7)
Histological grade	
1	6 (10.5)
2	35 (61.4)
3	16 (28.1)
Nuclear grade	
1	5 (8.8)
2	28 (49.1)
3	24 (42.1)
LVI	
Absent	57 (65.5)
Present	30 (34.5)
PNI	
Absent	70 (80.5)
Present	17 (19.5)
In situ	
0	51 (58.6)
1	34 (39.1)
2	2 (2.3)
ER status	
Positive	50 (89.3)
Negative	6 (10.7)
PR status	
Positive	43 (76.8)
Negative	13 (23.2)
CerbB2 status	
Negative	38 (66.7)
Positive	19 (21.8)
CerbB2 score	
0	25 (43.9)
1	13 (22.8)
2	2 (3.5)
3	17 (29.8)
Miller–Payne	
1	7 (8)
2	13 (14.9)
3	23 (26.4)
4	14 (16.1)
5	30 (34.5)
Pinder	
1	28 (32.6)
2	10 (11.6)
3	33 (38.4)
4	15 (17.4)
Tumor size (mm)	30.89±15.29 (9.5–86)
Number of foci	2.76±1.09 (2–6)
Ki-67 (%)	0.28±0.20 (0.02–0.85)

Data are presented as frequency (percentage) or mean ± standard deviation (minimum-maximum), IDC: Invasive ductal carcinoma, IIAB: Fine needle aspiration biopsy, LVI: Lymphovascular invasion, PNI: Perineural invasion, ER: Estrogen receptor, PR: Progesterone receptor, CerbB2: c-erbB-2

histopathology, molecular biology, and response to systemic therapies (1). As in many other malignancies, breast cancer has been classified into distinct subtypes to enable the development and implementation of tailored therapeutic regimens. Among the diverse forms of genetic damage, including DNA double-strand breaks, base substitutions, and mismatches, such alterations represent some of the most detrimental lesions that threaten cellular viability. To safeguard genomic stability, cells have evolved multiple repair pathways, the disruption of which plays a pivotal role in breast carcinogenesis (15).

One of these critical repair pathways is the DNA MMR system, which recognizes and corrects misincorporated bases that occur during DNA replication, recombination, or as a result of other genotoxic insults. The MMR system additionally addresses errors that escape the proofreading activity of DNA polymerase (16). Integrity of the MMR pathway is essential for maintaining genomic fidelity; however, given that several chemotherapeutic agents target this mechanism, tumors harboring MMR deficiency may acquire resistance, thereby complicating therapeutic strategies and adversely affecting clinical outcomes (17).

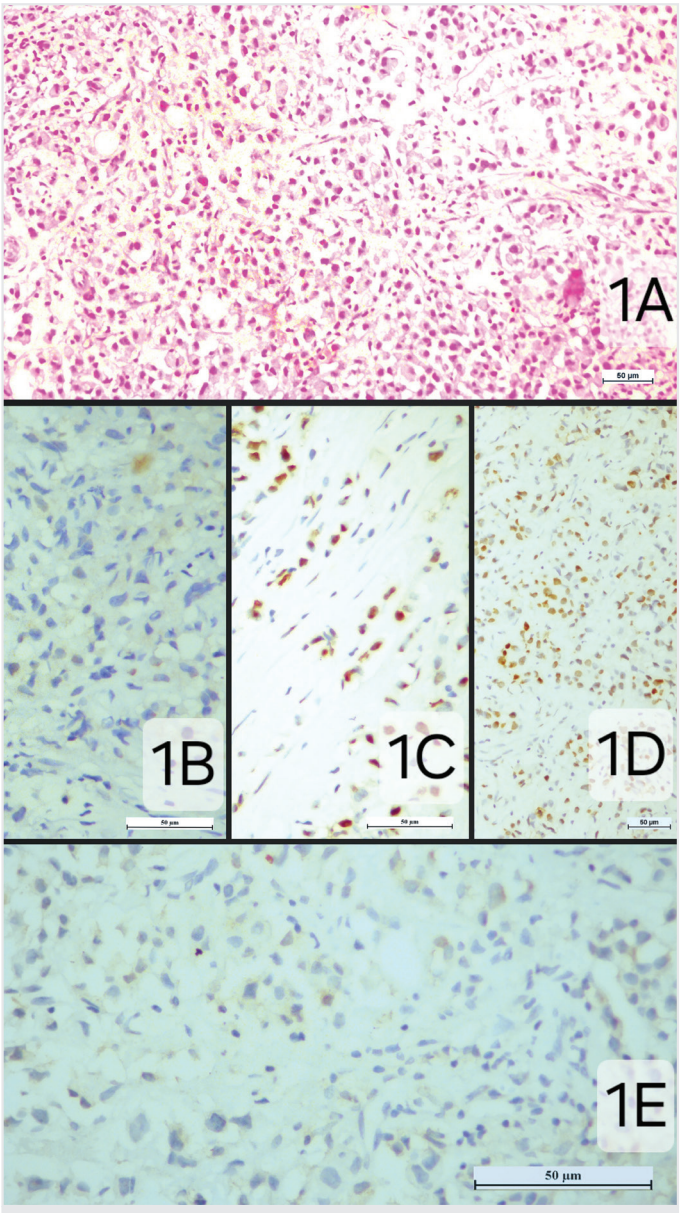

Figure 1. (A) Invasive ductal carcinoma (hematoxylin and eosin, × 200). (B) Loss of nuclear expression of PMS2 (IHC, × 400). (C) Nuclear staining for MSH2 (IHC, × 200). (D) Nuclear staining for MSH6 (IHC, × 400). (E) Loss of nuclear expression of MLH1 (IHC, × 400)

PMS2: Postmeiotic segregation increased 2, IHC: Immunohistochemistry, MSH2: MutS homolog 2, MSH6: MutS homolog 6, MLH1: MutL homolog 1

While MSI, a hallmark of defective MMR, has been extensively documented in colorectal, endometrial, and ovarian carcinomas, its prevalence, biological relevance, and prognostic value in breast carcinoma remain incompletely elucidated and are the subjects of ongoing investigation (18-21).

The aim of this study was to investigate the frequency of MSI in breast carcinoma and to evaluate its association with clinicopathological parameters. The findings of this study demonstrated that MSI had no significant correlation with clinicopathological variables or survival outcomes in breast carcinoma, suggesting that MSI may not be a strong prognostic or predictive biomarker in this tumor type.

Table 2. Comparison of relevant variables between MSS and MSI groups

Variable	MSS	MSI	p
Miller–Payne			
1	7 (100%)	0 (0%)	
2	13 (100%)	0 (0%)	0.802[a]
3	20 (87.0%)	3 (13.0%)	
4	13 (92.9%)	1 (7.1%)	
5	26 (89.7%)	3 (10.3%)	
Pinder			
1	26 (92.9%)	2 (7.1%)	
2	9 (100%)	0 (0%)	0.842[a]
3	29 (87.9%)	4 (12.1%)	
4	14 (93.3%)	1 (6.7%)	
ER (resection)			
Negative	6 (100%)	0 (0%)	1[a]
Positive	46 (92.0%)	4 (8.0%)	
PR (resection)			
Negative	13 (100%)	0 (0%)	0.254[a]
Positive	39 (90.7%)	4 (9.3%)	
CerbB2 score (resection)			
Negative	34 (89.5%)	4 (10.5%)	0.290[a]
Positive	19 (100%)	0 (0%)	
CerbB2 grade (resection)			
0	23 (92.0%)	2 (8.0%)	0.358[a]
1	11 (84.6%)	2 (15.4%)	
2	2 (100%)	0 (0%)	
3	17 (100%)	0 (0%)	
ER (biopsy)			
Negative	10 (100%)	0 (0%)	1[a]
Positive	69 (90.8%)	7 (9.2%)	
PR (biopsy)			
Negative	26 (96.3%)	1 (3.7%)	0.425[a]
Positive	53 (89.8%)	6 (10.2%)	
Molecular subtype			
1	11 (91.7%)	1 (8.3%)	
2	55 (90.2%)	6 (9.8%)	0.709[a]
3	4 (100%)	0 (0%)	
4	9 (100%)	0 (0%)	
Stromal lymphoid grade			
1	42 (89.4%)	5 (10.6%)	0.634[a]
2	22 (95.7%)	1 (4.3%)	
3	15 (93.8%)	1 (6.3%)	
Survival status			
Dead	16 (94.1%)	1 (5.9%)	0.704[a]
Alive	63 (91.3%)	6 (8.7%)	
CerbB2 score (biopsy)			
Negative	43 (89.6%)	5 (10.4%)	0.457[a]
Positive	36 (94.7%)	2 (5.3%)	

Table 2. Continued

Variable	MSS	MSI	p
CerbB2 grade (biopsy)			
0	22 (84.6%)	4 (15.4%)	0.456[a]
1	20 (95.2%)	1 (4.8%)	
2	2 (100%)	0 (0%)	
3	35 (94.6%)	2 (5.4%)	
Ki-67 (%) (resection)	0.20 (0.02–0.85)	0.30 (0.25–0.50)	0.205[a]
Ki-67 (%) (biopsy)	0.30 (0.10–0.80)	0.30 (0.10–0.50)	0.775[b]
Stromal lymphocytic response (%)	0.20 (0.10–0.80)	0.15 (0.10–0.90)	0.346[b]
Overall survival (months)	48 (2–108)	60 (24–108)	0.567[b]
Disease-free survival (months)	42 (0–108)	60 (24–108)	0.542[b]

Categorical data are presented as frequency (percentage), numerical data as median (minimum-maximum). [a]chi-square and [b]Mann Whitney U tests were used. MSS: Microsatellite stability, MSI: Microsatellite instability, ER: Estrogen receptor, PR: Progesterone receptor, CerbB2: c-erbB-2

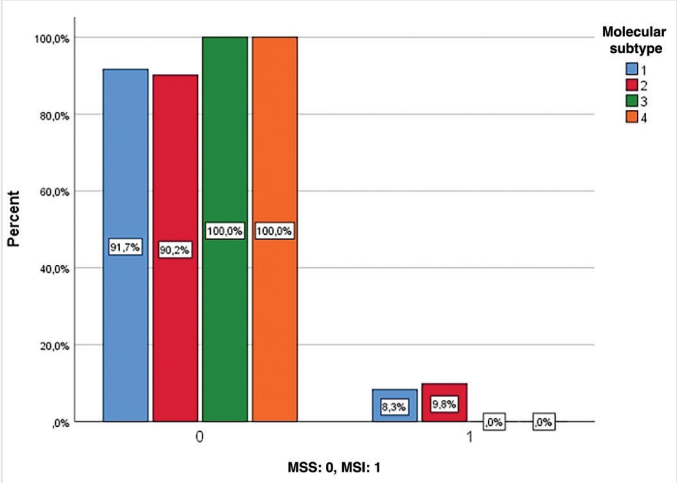

Figure 2. Distribution of molecular subtypes in MSS and MSI groups. Molecular subtype 1: Luminal A, 2: Luminal B, 3: Triple negative, 4: CerbB2
MSS: Microsatellite stability, MSI: Microsatellite instability, CerbB2: c-erbB-2

In our study, the prevalence of MSI was 8%, which is consistent with the findings reported in the literature (22). Data regarding the frequency of MSI in breast cancer are highly variable: some studies have reported a very low prevalence (below 1%), whereas others have documented higher rates, particularly in subtypes such as triple-negative breast cancer (23,24). For instance, one study conducted in patients with metastatic breast cancer reported an MSI prevalence of 0.63% (25). Such discrepancies may be attributed to factors including sample size, population heterogeneity, the methodologies employed for MSI detection, and differences in study design (26,27).

A large-scale study by Cheng et al. (28) that evaluated the relationship between MMR deficiency, breast cancer subtypes, and prognostic factors reported MMR deficiency in 1.9% of 1,635 cases assessed by immunohistochemistry. This study demonstrated that MMR deficiency was associated with a higher histological grade, lower PR expression, and a higher number of tumor-infiltrating lymphocytes. Moreover, among 431 ER–positive patients who received adjuvant systemic therapy with tamoxifen alone, MMR deficiency was significantly associated with poorer overall survival and disease-free survival (28). In contrast, our study found no statistically significant association between MMR status and histological grade, PR status, TIL percentage, or survival outcomes. The discrepancies between these findings may be attributed to differences in sample size, population characteristics, therapeutic approaches, and sampling methodologies.

Table 3. Comparison of relevant variables between MSS and MSI groups in resection

Variable	MSS	MSI	p
Localization			
1	38 (88.4%)	5 (11.6%)	0.433[a]
2	41 (95.3%)	2 (4.7%)	
Subtype			
IDC	69 (93.2%)	5 (6.8%)	0.155[a]
Lobular	6 (75%)	2 (25%)	
Mixed	4 (100%)	0 (0%)	
Quadrant			
Upper inner	10 (83.3%)	2 (16.7%)	0.197[a]
Upper outer	41 (95.3%)	2 (4.7%)	
Lower inner	13 (81.3%)	3 (18.7%)	
Lower outer	12 (100%)	0 (0%)	
Retroareolar	3 (100%)	0 (0%)	
Histological grade			
1	5 (83.3%)	1 (16.7%)	0.554[a]
2	33 (94.3%)	2 (5.7%)	
3	15 (93.8%)	1 (6.3%)	
Nuclear grade			
1	4 (80%)	1 (20%)	0.393[a]
2	26 (92.9%)	2 (7.1%)	
3	23 (95.8%)	1 (4.2%)	
LVI			
Absent	50 (89.3%)	6 (10.7%)	0.413[a]
Present	29 (96.7%)	1 (3.3%)	
PNI			
Absent	62 (89.9%)	7 (10.1%)	0.336[a]
Present	17 (100%)	0 (0%)	
In situ carcinoma			
0	47 (94%)	3 (6%)	0.552[a]
1	30 (88.2%)	4 (11.8%)	
2	2 (100%)	0 (0%)	
Age (years)	49 (31–74)	59 (49–63)	0.057[b]
Tumor size (mm, radiological)	28 (9.5–86)	29 (12–37)	0.962[b]
Number of foci	2.5 (2–6)	2 (2–2)	0.304[b]

Categorical data are presented as frequency (percentage), numerical data as median (minimum-maximum). [a]chi-square and [b]Mann-Whitney U tests were used. MSS: Microsatellite stability, MSI: Microsatellite instability, LVI: Lymphovascular invasion, PNI: Perineural invasion, IDC: Invasive ductal carcinoma

Table 4. Comparison of relevant variables between MSS and MSI groups in biopsy

Variable	MSS	MSI	p
Subtype			
IDC	70 (92.1%)	6 (7.9%)	0.593[a]
Lobular	6 (85.7%)	1 (14.3%)	
Mixed	3 (100%)	0 (0%)	
Histological grade			
1	6 (85.7%)	1 (14.3%)	0.365[a]
2	49 (94.2%)	3 (5.8%)	
3	24 (88.9%)	3 (11.1%)	
Nuclear grade			
1	5 (83.3%)	1 (16.7%)	0.266[a]
2	49 (94.2%)	3 (5.8%)	
3	25 (89.3%)	3 (10.7%)	
LVI			
Absent	55 (90.2%)	6 (9.8%)	0.668[a]
Present	24 (96%)	1 (4%)	
PNI			
Absent	73 (91.3%)	7 (8.8%)	1[a]
Present	6 (100%)	0 (0%)	
In situ			
0	64 (90.1%)	7 (9.9%)	0.653[a]
1	13 (100%)	0 (0%)	
2	2 (100%)	0 (0%)	
Necrosis			
Absent	71 (92.2%)	6 (7.8%)	0.552[a]
Present	8 (88.9%)	1 (11.1%)	

Categorical data are presented as frequency (percentage). [a]chi-square test was used. IDC: Invasive ductal carcinoma, LVI: Lymphovascular invasion, PNI: Perineural invasion, MSS: Microsatellite stability, MSI: Microsatellite instability

Table 5. Evaluation of survival time according to MSI and MSS status

Group	Estimate	Standard error	95% CI	p
MSS	88.53	4.29	80.12–96.94	0.659
MSI	93.60	12.88	68.35–118.84	

p value corresponds to Log-Rank test. CI: Confidence interval, MSS: Microsatellite stability, MSI: Microsatellite instability

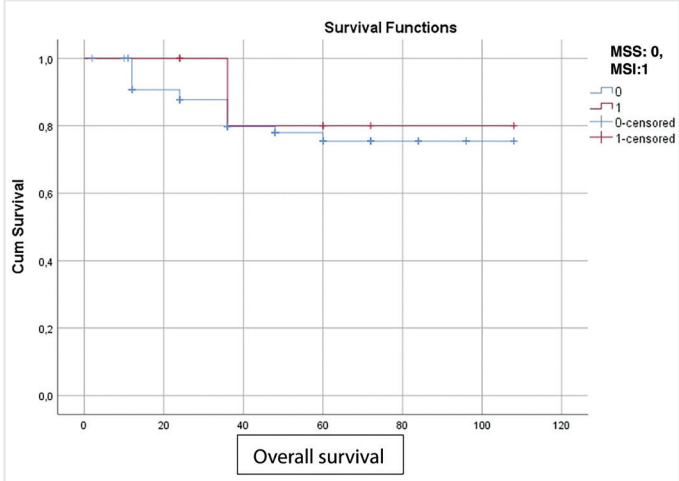

Figure 3. Overall survival according to MSI and MSS status
MSS: Microsatellite stability, MSI: Microsatellite instability

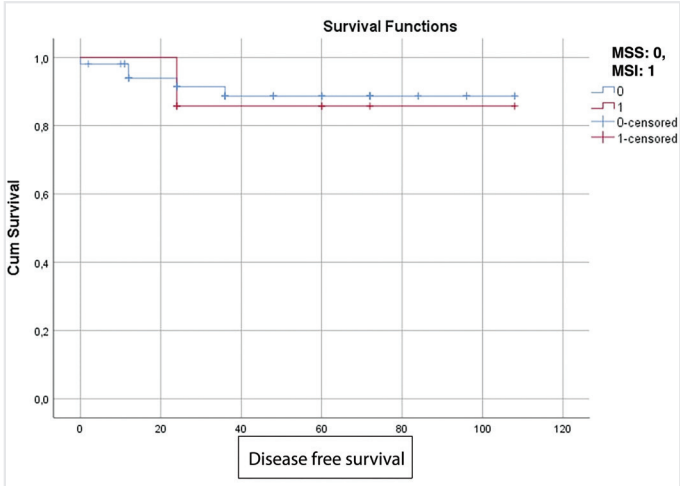

Figure 4. Disease-free survival according to MSI and MSS status
MSS: Microsatellite stability, MSI: Microsatellite instability

Table 6. Evaluation of disease-free survival time according to MSI and MSS status

Group	Estimate	Standard error	95% CI	p
MSS	97.84	4.29	89.42–106.26	0.806
MSI	96	11.11	74.22–117.77	

p value corresponds to Log-Rank test. CI: Confidence interval, MSS: Microsatellite stability, MSI: Microsatellite instability

In the study by Cheng et al. (28), MSI status was not found to be highly prevalent in any specific molecular subtype of breast cancer. Similarly, in our study, no significant association was observed between MSI status and molecular subtypes, which is consistent with the existing literature.

Although some studies have suggested that MSI may be associated with chemotherapy response in breast cancer, our study did not identify any statistically significant association between MSI status and histopathological parameters before and after chemotherapy, nor between MSI status and survival outcomes (4). In the study by Demokan et al. (6), MSI was similarly found to have no significant association with age, lymph node involvement, disease stage, tumor size, ER status, metastasis, family history, or histological and nuclear grades. Consistent with these findings, our study demonstrated no statistically significant association between MSI status and age, tumor subtype, localization, multifocality, histological and nuclear grades, LVI, PNI, metastatic status, ER, PR, CerbB2, or Ki-67 proliferation index.

These parallel findings suggest that the biological mechanisms by which MSI may contribute to breast carcinogenesis are incompletely understood, and that its prognostic and predictive significance in this tumor type is uncertain. This supports the broader observation that the prognostic and predictive value of MSI may vary considerably across different cancer types (17,29).

A high degree of concordance between IHC and molecular techniques in the detection of MMR deficiency has been consistently reported. Several studies have indicated that both IHC and molecular assays are highly effective and equally informative (30). Although our study employed only the IHC method, the similarity between our findings and those reported in the literature suggests that IHC is a widely applicable, cost-effective, and diagnostically reliable alternative in clinical practice.

In our study, no statistically significant differences were observed between the MSI and MSS groups with respect to the Miller–Payne classification, Pinder lymph node scoring system, ER, PR, Ki67, CerbB2, CerbB2 score, molecular subtype, stromal lymphocyte percentage, stromal lymphocyte grade, intratumoral lymphocytic response, overall survival, disease-free survival, recurrence or metastasis, or mortality status. Assessments were performed on both tru-cut biopsies and post-neoadjuvant resection specimens ($p>0.05$). Similarly, statistical analysis of resection specimens revealed no significant differences between MSI and MSS groups with respect to tumor size, histological subtype, age, tumor localization (quadrant), number of foci, histological grade, nuclear grade, LVI, PNI, or presence of carcinoma *in situ* ($p>0.05$). Furthermore, analysis of biopsy specimens demonstrated no significant association between MSI status and histological subtype, histological grade, nuclear grade, LVI, PNI, *in situ* carcinoma, or necrosis ($p>0.05$). Overall survival and disease-free survival also did not differ significantly according to MSI or MSS status ($p>0.05$).

These findings support the conclusion that MMR/MSI is not a robust prognostic or predictive biomarker in breast cancer.

Study Limitations

The main limitations of our study are its retrospective design and the relatively small sample size. Future research should aim to elucidate the role of MMR/MSI in breast cancer through larger, prospective cohort studies conducted in diverse ethnic populations that utilize standardized testing methodologies and evaluate specific chemotherapy regimens. In addition, the interactions between MMR status, the tumor microenvironment, and immune responses represent important areas that warrant further investigation.

Conclusion

This study aimed to determine the frequency of microsatellite instability in invasive breast carcinoma and to evaluate its associations with response to NACT, clinicopathological parameters, and survival outcomes. In our cohort, MSI was identified in 8% of cases. The principal finding of our study is that MSI status did not show a statistically significant association with any evaluated clinicopathological variable, including the Miller–Payne classification, Pinder lymph node scoring system, ER and PR status, Ki-67 proliferation index, CerbB2 expression, molecular subtype, stromal lymphocyte percentage/grade, intratumoral lymphocytic response, tumor size, histological grade, or lymphovascular/perineural invasion, nor with survival outcomes, namely overall survival and disease-free survival. These results suggest that within our cohort of patients with invasive breast carcinoma, MSI does not emerge as an independent prognostic or predictive biomarker.

Although MSI is widely recognized as a strong prognostic marker and predictor of response to immunotherapy in certain cancers, its role in breast cancer appears to be more complex and remains insufficiently clarified. While some studies have suggested that loss of MMR protein expression may serve as a prognostic and predictive biomarker in breast cancer, the findings of our study support the view that evidence does not consistently demonstrate MSI as a reliable prognostic or predictive marker in this tumor type. Despite the retrospective design and limited sample size, our results indicate that immunohistochemistry can be used as a practical approach for evaluating MMR protein expression in routine pathology.

Future investigations should further clarify the role of MSI/MMR alterations in breast cancer through larger, prospective cohort studies employing standardized testing methodologies and assessing their relationship with specific NACT regimens. Such comprehensive studies may contribute to the development of more personalized therapeutic approaches in the management of breast cancer.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Non-Interventional Scientific Research Ethics Committee of İstanbul Atlas University (approval number: 08/06, date: 29.09.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - Ö.G., E.Y., S.C.; Concept - Ö.G., S.B., E.Y., C.K.T.; Design - Ö.G., S.B., C.K.T.; Data Collection or Processing - Ö.G., S.B., M.C., S.C.; Analysis or Interpretation - Ö.G., S.B., E.Y., C.K.T.; Literature Search - Ö.G., S.B., M.C., S.C.; Writing - Ö.G., S.B., M.C., C.K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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