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Risk Factors and Survival Outcomes Associated with Breast Cancer Recurrence

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ABSTRACT

Breast cancer recurrence remains a major clinical challenge, despite advancements in diagnosis and treatment. Identifying reliable clinicopathological predictors is essential for improving long-term outcomes and guiding individualized treatment. **Objective:** To assess the clinicopathological characteristics and risk factors associated with breast cancer recurrence and evaluate survival outcomes in patients with operable breast cancer. **Methods:** This retrospective study included 281 patients diagnosed with operable primary breast cancer at a tertiary care center. Data were collected on demographic, histopathological, and treatment-related variables. Recurrence was defined as any documented local, regional, or distant relapse after initial treatment. Statistical analyses included chi-square tests for categorical variables and independent-samples t-tests for continuous variables to assess associations with recurrence. A p-value<0.05 was considered statistically significant. **Results:** The overall recurrence rate was 31.7 %, with distant metastasis being the most common type. Odds ratios with 95 % confidence intervals for categorical variables (molecular subtype, hormone receptor status, tumor size category, histological grade, Ki-67 index, and lymphovascular invasion) showed no statistically significant associations with recurrence. Likewise, mean differences with 95 % confidence intervals for continuous variables (age, tumor size, Ki-67 index, and disease-free survival) revealed no significant differences between recurrence and non-recurrence groups. **Conclusions:** No clinicopathological factor was found to be a statistically significant predictor of breast cancer recurrence in this cohort. These findings highlight the limitations of traditional pathological markers and underscore the need to integrate molecular and genomic profiling for more accurate recurrence risk assessment and personalized treatment planning.

INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer and the leading cause of cancer-related death among women worldwide. Despite advances in early detection and therapy, recurrence continues to be a major clinical concern, significantly affecting survival outcomes and quality of life [1-3]. Recurrence may occur locally, regionally, or as distant metastases, and is often influenced by a complex interplay of demographic, pathological, and molecular factors. Understanding the risk factors associated with breast cancer recurrence is critical for tailoring treatment strategies and improving long-term outcomes. Age has been shown to significantly impact recurrence and survival. Younger women, particularly those under 40, often present with more aggressive tumor subtypes and higher proliferation indices such as Ki-67, resulting in higher recurrence rates and

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worse disease-free survival (DFS) [4, 5]. Conversely, older age (>65) is associated with distinct recurrence patterns and often comorbidities that complicate prognosis and treatment [6]. Molecular subtype plays a pivotal role in recurrence patterns. Triple-negative breast cancer (TNBC) and HER2-positive subtypes are linked with higher recurrence risks and poorer prognosis compared to luminal A and B subtypes, which tend to recur later and are generally associated with better survival outcomes [4, 7]. A recent study found the time to recurrence was shortest in TNBC and HER2-positive patients, with longer recurrence-free intervals seen in hormone receptor-positive subtypes [6]. Pathological features such as tumor size, lymph node involvement, histologic and nuclear grade, and lymphovascular invasion (LVI) are also strong predictors of recurrence [1, 8]. A large meta-analysis of hormone receptor-positive, HER2-negative breast cancer patients in Japan revealed that lymph node metastasis and high tumor grade significantly reduced relapse-free survival [1]. Similarly, high Ki-67 expression has been shown to increase the likelihood of local or regional recurrence [9]. Treatment-related factors further influence survival and recurrence. Adjuvant chemotherapy, hormone therapy, and radiotherapy significantly reduce recurrence risk and improve survival when administered appropriately based on tumor characteristics [7, 10]. A study from Saudi Arabia reported that patients who did not receive adjuvant chemotherapy had significantly worse DFS and higher recurrence rates [3]. In addition, limited post-operative follow-up was also associated with a greater risk of recurrence, underlining the importance of long-term monitoring [3]. Recent advancements in predictive modeling have further enhanced recurrence risk stratification. Clinical risk scoring systems and machine learning models incorporating both molecular and clinical data have demonstrated promising accuracy in predicting recurrence and survival outcomes [9, 11]. Breast cancer recurrence remains a critical challenge despite advances in treatment, significantly impacting patient survival. While various risk factors like age, tumor subtype, and pathological features have been linked to recurrence, evolving therapies and population differences highlight the need for updated analysis.

This study aims to identify key predictors of recurrence and their effect on survival to help improve patient monitoring and treatment planning.

METHODS

This retrospective cohort study was conducted at the Department of Histopathology, Quaid-e-Azam Medical College, Bahawalpur, after obtaining approval from the Institutional Review Board (2507/DME/QAMC Bahawalpur). The study included breast cancer cases diagnosed and treated between January 2020 and June 2024. Data abstraction from hospital records, pathology reports, and follow-up registries was carried out for 3 months (August 2024 to October 2024) following IRB approval. The objective was to evaluate the risk factors associated with breast cancer recurrence and their impact on survival outcomes. The sample size was calculated using the formula: n = (Z^2 × p × (1 – p)) / d^2, where Z = 1.96 for a 95% confidence level, p=0.76 (the 5-year disease-free survival rate reported by Chen et al.), and d = 0.05 (5% margin of error). This yielded a required sample size of approximately 281 patients [4]. Eligible participants were female patients aged 18 years and above, with histologically confirmed primary breast carcinoma who had undergone definitive surgery, including either breast-conserving surgery or mastectomy. Patients with complete clinicopathological and follow-up records and a minimum follow-up period of six months were included. Written informed consent was taken. Exclusion criteria comprised those with metastatic disease at the time of diagnosis, recurrent breast cancer or second primary tumors, incomplete records, or patients lost to follow-up within six months after treatment. Data were collected retrospectively using a structured data abstraction form from hospital records, pathology reports, and follow-up registries. The predictor variables recorded included age at diagnosis, tumor size, lymph node involvement, histological grade, and molecular subtype (Luminal A/B, HER2-enriched, Triple-negative), which was assigned strictly using immunohistochemical (IHC) surrogates based on ER, PR, HER2, and Ki-67 status according to established criteria; no additional genomic profiling was performed. Hormone receptor status (estrogen and progesterone receptors), HER2 status, and Ki-67 proliferation index, which was recorded as a continuous percentage and, for subgroup analyses, categorized as low (≤20%) versus high (>20%) expression based on established guidelines, were also included. Additional variables included type of surgery, type of adjuvant therapies (chemotherapy, radiotherapy, hormone therapy), which were recorded to account for potential confounding effects of standardized multimodal treatment on recurrence risk, presence of lymphovascular invasion, and menopausal status. Outcome variables included recurrence status (yes/no), type of recurrence (local vs distant), time to recurrence, disease-free survival (DFS), and overall survival (OS). All data were entered and analyzed using IBM SPSS version 25.0. Descriptive statistics summarized patient demographics and clinical variables. Continuous variables were reported as mean ± standard deviation, and categorical variables as frequencies and percentages. For subgroup analysis, the Ki-67 proliferation index was dichotomized into low (≤20%) and high (>20%)

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expression. Associations between categorical variables (including Ki-67 category and adjuvant therapy type) and recurrence were analyzed using the Chi-square test or Fisher's exact test where appropriate. Differences in means of continuous variables between recurrence and non-recurrence groups were assessed using the independent samples t-test. Recurrence-free survival (RFS) was defined as the time from definitive surgery to the first documented local, regional, or distant recurrence or last follow-up. RFS was estimated using the Kaplan–Meier method, and survival distributions between groups were compared using the log-rank (Mantel–Cox) test. A p-value<0.05 was considered statistically significant.

RESULTS

A total of 281 patients were included in the analysis. The mean age at diagnosis was 51.74 ± 13.52 years, and the average tumor size was 5.47 ± 1.48 cm. The mean Ki-67 proliferation index was 33.37 ± 16.11%, indicating a moderate level of tumor cell proliferation across the cohort. The mean disease-free survival (DFS) duration was 41.72 ± 17.19 months. The study summarizes the frequency distribution of key clinicopathological variables among 281 breast cancer patients. A majority of tumors were histologically high grade, with Grade III reported in 172 (61.2%) patients, followed by Grade II in 93 (33.1%) and Grade I in only 16 (5.7%), indicating a predominance of aggressive histological profiles within the study cohort. In terms of molecular subtype, Luminal A was the most common, observed in 104 (37.0%) cases, followed by Luminal B in 72 (25.6%), and Triple-negative in 67 (23.8%). The HER2-enriched subtype was the least frequent, comprising 38 (13.5%) of the cases. This distribution suggests a notable proportion of hormone receptor-positive tumors, although a substantial number of patients also had more aggressive phenotypes such as triple-negative and HER2-enriched subtypes. Regarding hormone receptor status, estrogen receptor (ER) positivity was seen in 176 (62.6%) patients, while ER-negative tumors were identified in 105 (37.4%). Similarly, progesterone receptor (PR) positivity was found in 158 (56.2%) patients, compared to 123 (43.8%) who were PR-negative. HER2 overexpression was present in 86 (30.6%), while the remaining 195 (69.4%) were HER2-negative. These figures reflect a typical distribution pattern seen in operable breast cancer cases and support the clinical utility of targeted hormonal and HER2-based therapies. When evaluating adjuvant treatment modalities, 183 (65.1%) patients received a combination of chemotherapy, radiotherapy, and hormone therapy, representing a multimodal approach tailored to tumor biology. Chemo-radiotherapy without hormone therapy was administered in 61 (21.7%) cases, while chemotherapy alone was given to 34 (12.1%) patients. Only 3 (1.1%) patients did not receive any form of adjuvant therapy. This reflects a strong inclination toward comprehensive treatment regimens among the study population. Lymphovascular invasion (LVI), a known marker of poor prognosis, was present in 127 (45.2%) patients and absent in 154 (54.8%). This near-equal distribution suggests heterogeneity in tumor aggressiveness. In terms of disease outcomes, recurrence occurred in 89 (31.7%) patients, while 192 (68.3%) remained recurrence-free during the follow-up period. Among those who experienced recurrence, distant metastasis was more common, affecting 62 (22.1%), followed by local recurrence in 27 (9.6%) patients. These figures highlight that distant recurrence is the predominant mode of relapse in operable breast cancer and remains a major clinical challenge despite standard treatment. Using the predefined cut-off (≤20% for low expression and >20% for high expression), 72 patients (25.6%) were classified as having low Ki-67 expression and 209 patients (74.4%) as having high Ki-67 expression. This distribution indicates that the majority of tumors in this cohort exhibited a high proliferative index (Table 1).

Table 1: Frequency Distribution of Categorical Variables (n=281)

Variables	Category	n (%)
Histological Grade	Grade I	16 (5.7%)
	Grade II	93 (33.1%)
	Grade III	172 (61.2%)
Molecular Subtype	Luminal A	104 (37.0%)
	Luminal B	72 (25.6%)
	HER2-Enriched	38 (13.5%)
	Triple-Negative	67 (23.8%)
ER Status	Positive	176 (62.6%)
	Negative	105 (37.4%)
PR Status	Positive	158 (56.2%)
	Negative	123 (43.8%)
HER2 Status	Positive	86 (30.6%)
	Negative	195 (69.4%)
Adjuvant Therapy	Chemo + Radio + Hormone	183 (65.1%)
	Chemo + Radio	61 (21.7%)
	Chemo only	34 (12.1%)
	None	3 (1.1%)
Lymphovascular Invasion	Present	127 (45.2%)
	Absent	154 (54.8%)
Recurrence Status	Yes	89 (31.7%)
	No	192 (68.3%)
Type of Recurrence	Local	27 (9.6%)
	Distant	62 (22.1%)
	None	192 (68.3%)
Ki67 Category	Low (≤20%)	72 (25.6%)
	High (>20%)	209 (74.4%)

Findings summarize the association between clinicopathological variables and breast cancer recurrence, now including odds ratios (ORs) with 95 %

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confidence intervals to reflect effect size and precision. Across all evaluated categories, none of the associations reached statistical significance. For histological grade, recurrence occurred in 5 (31.3 %) patients with Grade I, 28 (30.1 %) with Grade II, and 56 (32.6 %) with Grade III tumors. Compared with Grade I, the odds of recurrence were similar for Grade II (OR 0.95, 95 % CI 0.30–2.98) and Grade III (OR 1.06, 95 % CI 0.35–3.20; p=0.919). Among molecular subtypes, recurrence was most frequent in Luminal A cases (38 (36.5 %)), followed by HER2-enriched (12 (31.6 %)), triple-negative (21 (31.3 %)), and Luminal B (18 (25.0 %)). Compared with Luminal A, the odds of recurrence were lower for Luminal B (OR 0.58, 95 % CI 0.30–1.13), HER2-enriched (OR 0.80, 95 % CI 0.36–1.77), and triple-negative (OR 0.79, 95 % CI 0.41–1.52; overall p=0.454). Regarding hormone receptor status, recurrence occurred in 55 (31.3 %) of ER-positive and 34 (32.4 %) of ER-negative patients (OR 1.05, 95 % CI 0.63–1.77; p=0.844), and in 51 (32.3 %) of PR-positive versus 38 (30.9 %) of PR-negative patients (OR 0.94, 95 % CI 0.56–1.56; p=0.805). Similarly, HER2-positive tumors showed 31 recurrences (36.0 %) compared with 58 (29.7 %) in HER2-negative tumors (OR 1.33, 95 % CI 0.78–2.28; p=0.295), indicating no significant difference. When examining adjuvant therapy, recurrence rates were 55 (30.1 %) among those receiving chemo + radio + hormone therapy, 20 (32.8 %) for chemo + radio, 13 (38.2 %) for chemo only, and 1 (33.3 %) for no adjuvant treatment. Compared with the multimodal group, the odds of recurrence were 1.14 (95 % CI 0.61–2.11) for chemo + radio and 1.44 (95 % CI 0.67–3.08) for chemo only (p=0.817). Interestingly, lymphovascular invasion showed recurrence in 35 (27.6 %) patients with LVI present versus 54 (35.1%) without LVI, corresponding to an OR of 1.42 (95 % CI 0.85–2.37; p=0.178). Although counterintuitive, this trend remained statistically non-significant and may reflect treatment confounding or variable follow-up durations. Finally, using the ≤20 % cut-off for Ki-67 expression, 20 of 72 patients (27.8 %) with low Ki-67 experienced recurrence compared to 69 of 209 (33.0 %) with high Ki-67 expression (OR 1.28, 95 % CI 0.71–2.31; p=0.410). This indicates no measurable association between Ki-67 category and recurrence status in this cohort. Overall, the inclusion of odds ratios with confidence intervals confirms that none of the clinicopathological factors evaluated showed a statistically significant association with recurrence (Table 2).

Table 2: Association of Clinicopathological Variables with Recurrence Status (n=281)

Variable (Reference Category)	Recurrence: Yes n (%)	Recurrence: No n (%)	OR (95 % CI)	p-Value
Histological Grade				
Grade II vs Grade I	28 (30.1) vs 5 (31.3)	65 (69.9) vs 11 (68.7)	0.95 (0.30–2.98)	0.919
Grade III vs Grade I	56 (32.6) vs 5 (31.3)	116 (67.4) vs 11 (68.7)	1.06 (0.35–3.20)	0.919
Molecular Subtype (vs Luminal A)				
Luminal B	18 (25.0) vs 38 (36.5)	54 (75.0) vs 66 (63.5)	0.58 (0.30–1.13)	0.454
HER2-Enriched	12 (31.6) vs 38 (36.5)	26 (68.4) vs 66 (63.5)	0.80 (0.36–1.77)	0.454
Triple-Negative	21 (31.3) vs 38 (36.5)	46 (68.7) vs 66 (63.5)	0.79 (0.41–1.52)	0.454
ER Status (Negative vs Positive)	34 (32.4) vs 55 (31.3)	71 (67.6) vs 121 (68.8)	1.05 (0.63–1.77)	0.844
PR Status (Negative vs Positive)	38 (30.9) vs 51 (32.3)	85 (69.1) vs 107 (67.7)	0.94 (0.56–1.56)	0.805
HER2 Status (Positive vs Negative)	31 (36.0) vs 58 (29.7)	55 (64.0) vs 137 (70.3)	1.33 (0.78–2.28)	0.295
Adjuvant Therapy (vs Chemo + Radio + Hormone)				
Chemo + Radio	20 (32.8) vs 55 (30.1)	41 (67.2) vs 128 (69.9)	1.14 (0.61–2.11)	0.817
Chemo Only	13 (38.2) vs 55 (30.1)	21 (61.8) vs 128 (69.9)	1.44 (0.67–3.08)	0.817
Lymphovascular Invasion (Absent vs Present)	54 (35.1) vs 35 (27.6)	100 (64.9) vs 92 (72.4)	1.42 (0.85–2.37)	0.178
Ki-67 Category (High >20 % vs Low ≤20 %)	69 (33.0) vs 20 (27.8)	140 (67.0) vs 52 (72.2)	1.28 (0.71–2.31)	0.410

OR = Odds Ratio for recurrence in the category shown compared with the reference category.

The study compares continuous clinicopathological variables between patients who experienced recurrence and those who did not, now including mean differences with 95 % confidence intervals. None of the variables demonstrated a statistically significant difference between the two groups. The mean age at diagnosis was slightly higher in the recurrence group (53.11 ± 13.69 years) than in the non-recurrence group (51.11 ± 13.43 years), but the mean difference of +2.00 years (95 % CI –1.44 to +5.44) was not statistically significant (p=0.249). Tumor size was marginally smaller in the recurrence group (5.23 ± 1.50 cm) compared to the non-recurrence group (5.59 ± 1.46 cm), with a mean difference of –0.36 cm (95 % CI –0.74 to +0.02; p=0.059), approaching but not reaching statistical significance. The Ki-67 proliferation index was comparable between groups (33.92 ± 15.79 % vs 33.11 ± 16.28 %), with a mean difference of +0.81 % (95 % CI –3.22 to +4.84; p=0.698). Disease-free survival (DFS) duration was virtually identical (41.67 ± 16.72 vs 41.73 ± 17.45 months), with a mean difference of –0.06 months (95 % CI –4.34 to +4.22; p=0.978).

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Overall, these findings show that none of the continuous baseline variables examined were significantly associated with recurrence, and the inclusion of mean differences with confidence intervals confirms the absence of clinically meaningful differences between groups (Table 3).

Table 3: Comparison of Continuous Variables Between Recurrence Groups (n=281)

Variables	Recurrence, Yes (n=89), Mean ± SD	Recurrence, No (n=192), Mean ± SD	Mean Difference (95 % CI)*	p-Value
Age at Diagnosis (Years)	53.11 ± 13.69	51.11 ± 13.43	+2.00 (-1.44 to +5.44)	0.249
Tumor Size (cm)	5.23 ± 1.50	5.59 ± 1.46	-0.36 (-0.74 to +0.02)	0.059
Ki-67 Index (%)	33.92 ± 15.79	33.11 ± 16.28	+0.81 (-3.22 to +4.84)	0.698
DFS (Months)	41.67 ± 16.72	41.73 ± 17.45	-0.06 (-4.34 to +4.22)	0.978

*Mean difference

Recurrence-free survival (RFS) was further evaluated using Kaplan–Meier analysis, which demonstrated a steady decline in RFS over time with a median RFS of approximately 41 months. No statistically significant differences in RFS were observed across molecular subtypes, histological grades, or lymphovascular invasion groups (log-rank p>0.05 for all comparisons), calculated as Recurrence Yes Minus Recurrence No. Tick marks indicate censored observations (Figure 1).

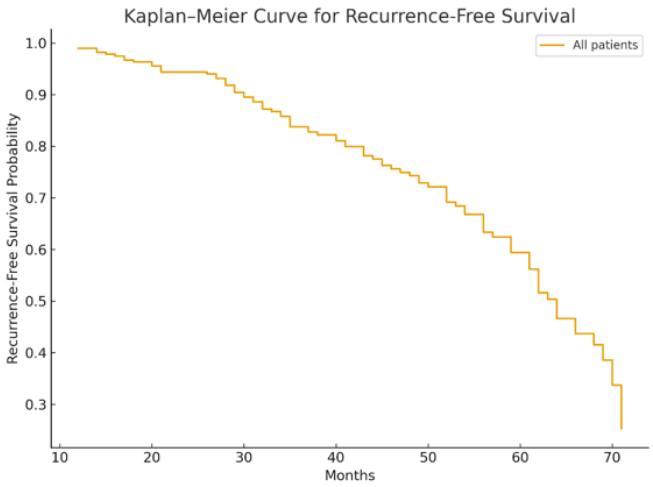

Figure 1: Kaplan–Meier Curve Showing RFS among 281 Patients with Operable Breast Cancer

DISCUSSIONS

This study analyzed recurrence patterns in a cohort of 281 breast cancer patients by evaluating a wide range of clinicopathological variables. The observed recurrence rate of 31.7% aligns with previous findings in similar cohorts, particularly among patients with aggressive molecular subtypes such as HER2-enriched and triple-negative breast cancer [12]. However, in our study, molecular subtype was not statistically associated with recurrence. Although recurrence was numerically more frequent in Luminal A and HER2-enriched tumors, these differences were not significant. This lack of association may be due to uniform application of treatment modalities across subtypes or unmeasured biological heterogeneity. The Ki-67 proliferation index showed a mean of 33.37%, reflecting moderate tumor proliferation overall. Yet, there was no significant difference in Ki-67 levels between recurrence and non-recurrence groups, consistent with studies reporting its limited predictive value when used independently [13]. While Ki-67 has been recognized as a marker of biological aggressiveness, its prognostic utility improves when integrated into multigene assays such as Oncotype DX, which better stratify recurrence risk in hormone receptor-positive breast cancer [14]. None of the traditional clinicopathological variables, including histological grade, hormone receptor status, HER2 expression, lymphovascular invasion, or type of adjuvant therapy, showed a statistically significant association with recurrence. These findings support previous research suggesting that individual pathological markers may have limited prognostic value in isolation, especially in the era of comprehensive multimodal treatment [15, 16]. An unexpected observation was the higher recurrence rate in patients without lymphovascular invasion (35.1%) compared to those with LVI (27.6%), though this trend was not statistically significant (p=0.178). This finding contradicts established literature that classifies LVI as an adverse prognostic factor [15, 16] and may be influenced by confounding factors such as tumor biology, differential follow-up, or treatment intensity. Further large-scale studies are needed to explore this paradox. Continuous variables, including age, tumor size, Ki-67 index, and DFS, also showed no significant differences between recurrence and non-recurrence groups. Interestingly, tumor size was marginally smaller in the recurrence group, though the difference approached but did not reach significance (p=0.059). This may suggest the influence of molecular or genetic factors not captured by baseline pathology alone. The nearly identical DFS duration between groups reinforces the concept that standard clinicopathological features may not sufficiently explain individual recurrence risk [17]. Furthermore, the lack of significant difference in recurrence across adjuvant therapy groups may reflect the equalizing effect of standardized, multimodal treatment regimens. This is consistent with previous studies indicating that, when systemic therapy is appropriately administered, recurrence rates can be similar across surgical modalities and molecular subtypes [18]. Overall, while recurrence rates varied across clinical subgroups, no statistically significant predictors emerged in our analysis. These findings underscore the limitations of relying solely on conventional clinicopathological markers and support the

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integration of molecular profiling, tumor microenvironment characteristics, and emerging biomarkers to improve recurrence risk prediction in breast cancer management [19–22].

CONCLUSIONS

In this study involving 281 patients with operable breast cancer, no clinicopathological variable, including tumor grade, molecular subtype, hormone receptor status, HER2 expression, tumor size, Ki-67 index, or lymphovascular invasion, demonstrated a statistically significant association with recurrence. Additionally, none of the continuous parameters, such as age, tumor size, Ki-67 index, or disease-free survival, differed significantly between recurrence groups. These findings highlight the limitations of relying solely on traditional pathological markers for recurrence prediction and underscore the need for incorporating molecular profiling and personalized risk assessment tools into clinical practice to enhance prognostication and guide individualized treatment strategies.

Authors Contribution

Conceptualization: SSG
Methodology: SSG, SS
Formal analysis: SSG
Writing review and editing: MSU, MS, SS, BM, BN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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