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ORIGINAL RESEARCH

Prognostic Value of Distant Micrometastasis in Breast Cancer: A Population-Based Propensity Score-Matched Study

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Background: Distant micrometastasis of breast cancer [M0(i+)] is an emerging metastatic stage that has not yet received widespread attention. This study aimed to compare M0(i+) patients with traditional M0 patients and to evaluate the prognostic value of M0(i+).

Methods: Using data from the SEER database (2018–2022), we identified 283,503 M0 patients and 585 M0(i+) patients. Propensity score matching (PSM) was applied to control for confounding factors in intergroup comparisons. Overall survival (OS) and breast cancer–specific mortality (BCSM) were assessed using the Kaplan–Meier method, Cox regression analysis, the cumulative incidence function (CIF), and the Fine–Gray competing risk model.

Results: After matching, no statistically significant differences were observed between the M0(i+) and M0 groups in either OS or BCSM (OS: HR=0.803, P=0.369; BCSM: HR=1.273, P=0.450). Nevertheless, the M0(i+) group showed a slightly worse survival trend in BCSM, while demonstrating a survival advantage in OS. This advantage may be influenced by the higher proportion of non–cancer-related deaths in this group.

Conclusion: The prognosis of M0(i+) patients is similar to that of M0 patients, supporting the rationale for combining the two stages in the AJCC staging system. Although the differences did not reach statistical significance, M0(i+) may still carry potential adverse prognostic implications. In light of prior literature, further refinement of the M0(i+) classification should be considered, with particular attention to the prognostic role of bone marrow micrometastasis.

Keywords: breast cancer, distant micrometastasis, AJCC, prognostic value, SEER

Introduction

Tumor metastasis refers to the process by which cancer cells detach from the primary lesion and establish secondary foci in distant organs.[1] The majority of cancer-related deaths do not result from the primary tumor itself but from metastatic disease.[2] Breast cancer is the most common malignancy among women,[3–5] and it is estimated that approximately 90% of breast cancer–related deaths are attributable to distant metastasis.[6] Clinically detectable distant metastasis has traditionally been considered a critical indicator of poor prognosis, with the liver, lung, brain, and bone being the most frequent and well-studied metastatic sites.[7–9]

With advances in technology, the presence of tumor cells can now be identified through microscopic examination and molecular techniques. Previous studies have demonstrated that micrometastases in the bone marrow and peripheral blood are strongly associated with unfavorable survival outcomes.[10–12] In 2010, the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual first introduced M0(i+) as a new subcategory under the M0 stage,[13] which was retained in the 8th edition released in 2017.[14] M0(i+) is defined as the presence of isolated tumor cells no larger than 0.2 millimeter (mm) in the

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bone marrow, peripheral blood, or non-regional lymph nodes, detected either microscopically or by molecular assays. However, clinical research and attention regarding M0(i+) remain limited, and its staging rationale and clinical significance have not been fully elucidated. Given the absence of an official or widely accepted nomenclature, and to distinguish it from conventional regional lymph node and distant metastases, we refer to M0(i+) in this study as "distant micrometastasis."In this study, we conducted the first large-scale population-based analysis of breast cancer patients with distant micrometastasis. By applying propensity score matching to minimize potential confounding, we aimed to more precisely evaluate the prognostic impact of distant micrometastasis, thereby providing insights for the refinement of future staging systems and clinical decision-making.

Methods

Data Source and Extraction

This study was conducted using data from the Surveillance, Epidemiology, and End Results (SEER) program, a national cancer database in the United States. Because breast cancer patients with M0(i+) disease were extremely rare prior to 2018, we extracted data from 2018 to 2022 using SEER*Stat software (Incidence – SEER Research Data, 17 Registries, Nov 2024 Sub [2000–2022]), downloaded from the official SEER website. This dataset covers 17 cancer registries across the US, representing approximately 26.5% of the national population, and is considered to have strong representativeness and generalizability.

The study cohort consisted of breast cancer patients classified as M0 or M0(i+) according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. We extracted demographic variables (sex, age at diagnosis), tumor pathological characteristics (maximum tumor diameter [mm], histologic type, grade), molecular markers (estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]), molecular subtype, AJCC staging (T/N/M), and prognostic information (vital status, survival time, and cause of death).

Inclusion and Exclusion Criteria

To ensure data accuracy and comparability of study results, we established the following criteria:

Inclusion Criteria

- Female breast cancer patients aged 18–89 years;
- Complete clinical and pathological information;
- Clear record of cause of death.

Exclusion Criteria

- Age <18 years or >89 years;
- Male patients;
- Grade classified as unassessable/unknown (9), undifferentiated (D), or nuclear grade (L/M/H);
- Cases with T stage of Tis or T0.

Variable Grouping

For analytical purposes, several variables were categorized and consolidated as follows:

- Histologic type: classified into invasive ductal carcinoma (IDC) and "other," with IDC including both IDC and ductal–lobular mixed carcinoma.
- Grade: classified as grade I–II and grade III.
- T stage: grouped into T1–T2 and T3–T4.
- N stage: grouped into N0 and N1–N3.

Survival Outcomes

The SEER database records causes of death; therefore, breast cancer–specific mortality (BCSM) was designated as the primary outcome to more precisely evaluate the adverse impact of breast cancer itself on survival. Overall survival (OS) was set as the secondary outcome, reflecting the risk of all-cause mortality.

Statistical Analysis

We first compared the clinicopathological characteristics between all M0 and M0(i+) patients. Given the much smaller sample size of the M0(i+) group, propensity score matching (PSM) was applied to minimize potential confounding in survival analyses.

Propensity scores were estimated using logistic regression, incorporating the following covariates: age, tumor size, histologic type, grade, ER, PR, HER2, molecular subtype, AJCC T stage, and AJCC N stage. Matching was performed with the nearest-neighbor method at a ratio of 1:2 (each M0(i+) patient matched with two M0 patients), using a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. Matching was conducted without replacement to avoid reuse of control subjects. After matching, clinicopathological characteristics between groups were re-compared to verify balance.

For survival analyses, OS was evaluated using the Kaplan–Meier method with the Log rank test, and hazard ratio (HR) with 95% confidence interval (CI) were estimated via the Cox proportional hazards regression model. For BCSM, the cumulative incidence function (CIF) and Fine–Gray competing risk model were additionally applied to account for non–breast cancer deaths as competing events. Differences in CIF curves between groups were assessed using the Gray test.

All statistical analyses and figure generation were performed using R software (version 4.3.1) on the RStudio platform. Data extraction, cleaning, and analysis were conducted from July to August 2025. The overall study flow is presented in Figure 1.

Results

Clinicopathological Characteristics Before Matching

A total of 324,571 breast cancer patients were extracted from the SEER database, including 323,891 M0 patients and 680 M0(i+) patients. Among the final cohort of 283,503 M0 and 585 M0(i+) patients, the median follow-up time (interquartile range, IQR) was 26 (12–42) months, with a maximum of 59 months. The median age of the M0(i+) group was significantly younger than that of the M0 group [61 years (IQR 52–70) vs 63 years (IQR 53–72), P = 0.002] (Table 1). No statistically significant differences were observed between the two groups with respect to tumor size, histologic type, grade, ER status, PR status, HER2 status, molecular subtype, or T stage (all P > 0.05). For N stage, the proportion of N1–N3 patients was higher in the M0(i+) group compared with the M0 group (29.23% vs 26.10%), with a borderline difference (P = 0.085).

Propensity Score Matching Results and Balance Assessment

Before matching, several variables showed standardized mean differences (SMD) > 0.1, such as distance variable (SMD = 0.1779) and age (SMD = –0.1322), indicating baseline imbalance. Although N stage (SMD = 0.0689) did not exceed the threshold, it approached the cutoff. After matching, 585 M0(i+) patients and 1,170 matched M0 patients were included. All covariates demonstrated SMD values < 0.1, with most within 0.05, and the distance variable reduced to 0, suggesting substantial balance improvement. Variance ratios of variables were close to 1, further validating the matching performance.

Changes in SMD values before and after matching are presented in Figure 2, showing that all covariates after matching fell within the SMD = 0.1 threshold, visually confirming improved balance. Post-matching clinicopathological characteristics also showed no statistically significant intergroup differences (all P > 0.05) (Table 2). Overall, PSM effectively minimized baseline differences, enhancing comparability and robustness of subsequent survival analyses.

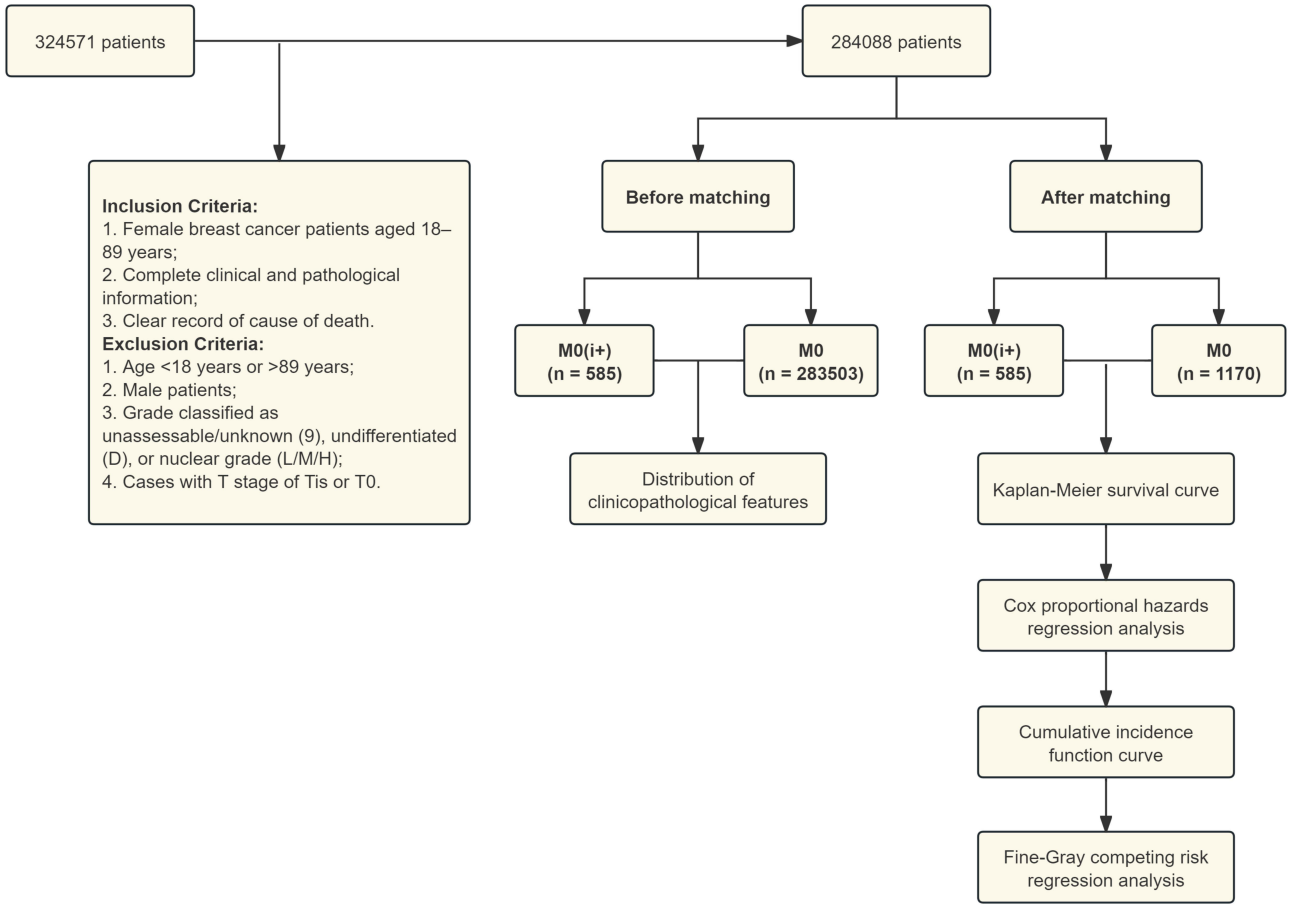

Figure 1 Study flowchart. All the bolded texts have no special meaning.

Overall Survival in Breast Cancer

After matching, the median follow-up (IQR) was 30 (18–47) months, with a maximum of 59 months. Among the matched cohort of 1,755 patients, 82 all-cause deaths were recorded. Kaplan–Meier analysis (Figure 3) revealed no significant difference in OS between the M0(i+) and M0 groups (P = 0.78), indicating comparable survival.

Univariable Cox regression (Table 3) showed that OS did not differ significantly between the M0(i+) and M0 groups (HR = 0.803, 95% CI = 0.498–1.296, P = 0.369). In contrast, older age, larger tumor size, higher grade, and regional lymph node metastasis were significantly associated with worse OS. Multivariable analysis further confirmed that after adjusting for age, tumor size, grade, and N stage, M0(i+) status was not an independent prognostic factor (HR = 0.805, 95% CI = 0.501–1.294, P = 0.370), while age, tumor size, grade, and N stage remained independent predictors of poor OS. These findings suggest that the prognosis of M0(i+) patients is comparable to that of M0 patients, with survival mainly determined by traditional factors.

Breast Cancer–Specific Mortality

Among 1,755 patients, 47 breast cancer–specific deaths and 35 non–breast cancer deaths (competing events) were observed. CIF analysis (Figure 4) showed no significant difference in BCSM between the M0(i+) and M0 groups (P = 0.27), indicating similar outcomes.

Univariable competing risk regression (Table 4) showed no significant difference in BCSM between the two groups (HR = 1.386, 95% CI = 0.775–2.480, P = 0.272). Significant predictors included age, tumor size, grade, ER/PR status, specific molecular subtypes, T stage, and N stage. Multivariable analysis further confirmed that M0(i+) status remained non-significant (HR = 1.273, 95% CI = 0.679–2.390, P = 0.450), suggesting no independent prognostic impact after

Table 1 Clinicopathological Characteristics of M0 and M0(i+) Patients Before Matching

Variable	M0 (n = 283,503)	M0(i+) (n = 585)	*P* value
Age, median (IQR), years	63 (53–72)	61 (52–70)	**0.002**
Tumor size, median (IQR), mm	16 (10–26)	16 (10–27)	0.617
Histologic type, n (%)			0.696
– IDC	239,129 (84.35%)	490 (83.76%)	
– Other	44,374 (15.65%)	95 (16.24%)	
Grade, n (%)			0.368
– I–II	202,498 (71.43%)	408 (69.74%)	
– III	81,005 (28.57%)	177 (30.26%)	
ER status, n (%)			0.785
– Negative	41,351 (14.59%)	83 (14.19%)	
– Positive	242,152 (85.41%)	502 (85.81%)	
PR status, n (%)			0.652
– Negative	70,889 (25.00%)	151 (25.81%)	
– Positive	212,614 (75.00%)	434 (74.19%)	
HER2 status, n (%)			0.908
– Negative	247,609 (87.34%)	510 (87.18%)	
– Positive	35,894 (12.66%)	75 (12.82%)	
Breast subtype, n (%)			0.995
– HR+/HER2-	218,830 (77.19%)	450 (76.92%)	
– HR+/HER2+	25,788 (9.10%)	53 (9.06%)	
– HR-/HER2+	10,106 (3.56%)	22 (3.76%)	
– HR-/HER2-	28,779 (10.15%)	60 (10.26%)	
Stage T, n (%)			0.815
– T1–T2	263,907 (93.09%)	546 (93.33%)	
– T3–T4	19,596 (6.91%)	39 (6.67%)	
Stage N, n (%)			0.085
– N0	209,521 (73.90%)	414 (70.77%)	
– N1–N3	73,982 (26.10%)	171 (29.23%)	

Notes: The bolded P value indicates significant statistical significance ($p < 0.05$), while the other bolded texts have no specific meaning.

Abbreviations: IQR, interquartile range; mm, millimeter; IDC, invasive ductal carcinoma; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

adjustment. In contrast, age, tumor size, ER status, certain breast cancer subtypes, and N stage remained independent adverse prognostic factors.

It is noteworthy that in both Cox and competing risk regression analyses, some molecular markers and HER2-related subtypes yielded extremely high HR values, and in Cox regression, certain 95% CIs approached infinity. This may be attributable to the relatively small number of events (82 deaths) in the matched cohort, limited sample size, and uneven event distribution.

Discussion

Our study demonstrated that, in terms of clinicopathological features, patients in the M0(i+) group were significantly younger than those in the M0 group (61 vs 63 years, P = 0.002). Although the proportion of regional lymph node metastasis was higher in the M0(i+) group compared with the M0 group (29.23% vs 26.10%), the difference did not reach statistical significance (P = 0.085). After 1:2 propensity score matching, differences in baseline characteristics between the two groups were further balanced, thereby reducing the potential confounding effect on prognosis. Multivariable analyses after matching revealed that the prognosis of M0(i+) patients was comparable to that of M0 patients for both OS (HR = 0.803, P = 0.369) and BCSM (HR = 1.273, P = 0.450). Notably, although the differences

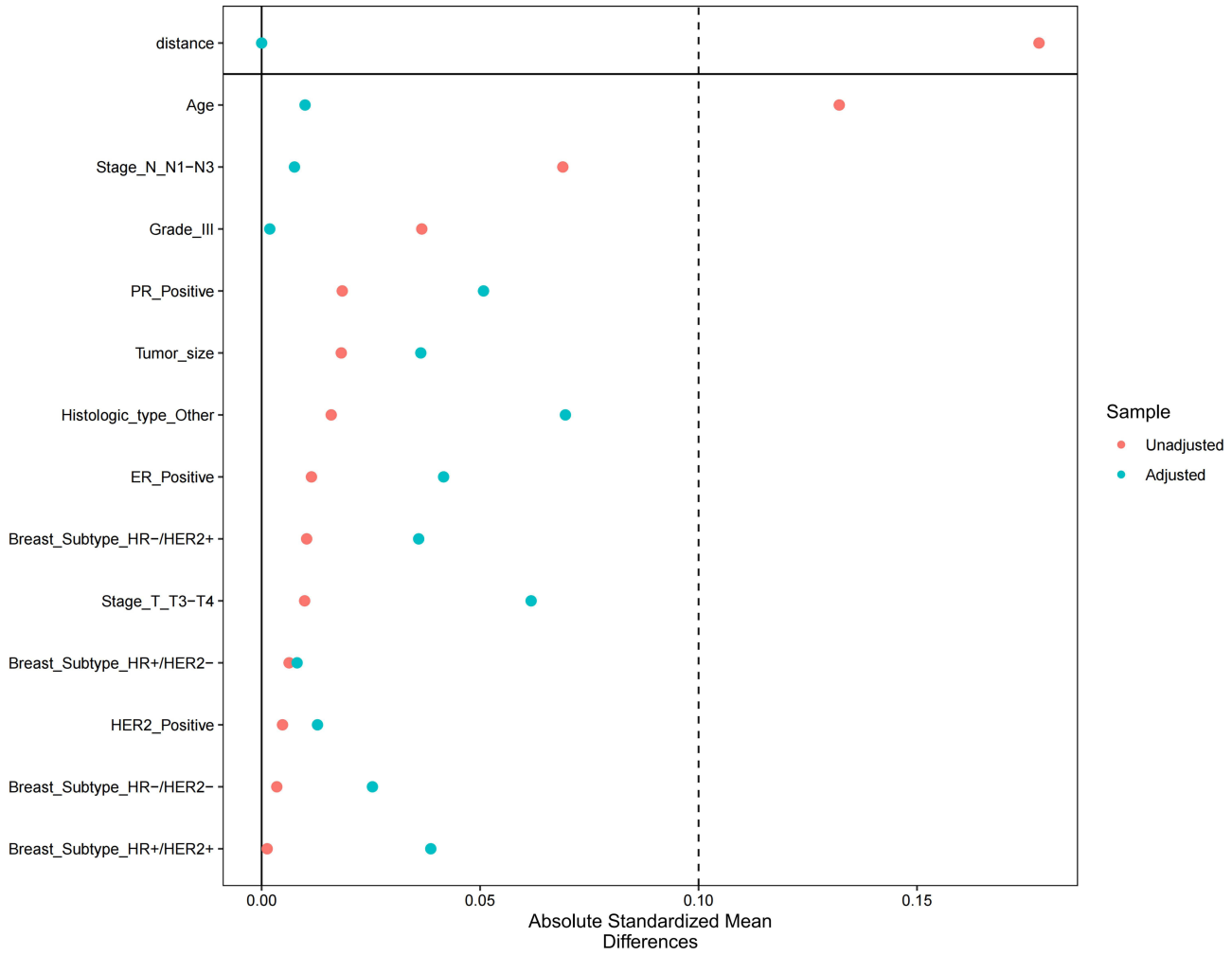

Figure 2 The changes in the standardized mean differences of each variable before and after matching.

were not statistically significant, the HR > 1 for BCSM suggests that M0(i+) status may potentially be associated with worse outcomes. In contrast, OS analysis showed an HR < 1, superficially indicating a survival advantage. We speculate that this result may be influenced by competing risks: among 82 deaths, 35 were attributable to non–cancer-related causes, which may have partially masked the potential adverse prognostic value of M0(i+).

Taken together, results from both OS and BCSM analyses suggest that M0(i+) may carry some unfavorable prognostic implications; however, the overall differences were not statistically significant. Therefore, the inclusion of M0(i+) within the M0 stage in the 7th and 8th editions of the AJCC staging system appears reasonable. From a clinical perspective, the survival outcomes of M0(i+) patients are similar to those of M0 patients, indicating that such patients may be managed according to strategies for localized breast cancer—receiving comprehensive treatment centered on curative surgery—rather than being treated as stage M1 cases requiring palliative management.

Although this is the first study to explore the prognostic value of distant micrometastasis in breast cancer based on the AJCC staging definition, previous research has already investigated the prognostic significance of bone marrow micrometastases, isolated tumor cells (ITCs) in the bone marrow, and circulating tumor cells (CTCs) in peripheral blood. In fact, the AJCC definition of M0(i+) already encompasses traditional micrometastases (greater than 0.2 mm but not exceeding 2 mm) as well as ITCs (smaller than 0.2 mm and/or fewer than 200 cells).[12,15] CTCs, by contrast, are defined as nucleated cells with a diameter >4 μm that express epithelial markers such as epithelial cell adhesion molecule (EpCAM) and cytokeratins (CK8, CK18, CK19), but lack expression of the leukocyte marker cluster of differentiation (CD)45.[16] Therefore, from a broad perspective, CTCs can also be considered as part of the M0(i+) category.

Table 2 Comparison of Clinicopathological Characteristics Between M0 and M0 (i+) Patients After Matching

Variable	M0 (n = 1,170)	M0(i+) (n = 585)	*P* value
Age, median (IQR), years	61 (52–69)	61 (52–70)	0.726
Tumor size, median (IQR), mm	16 (10–27)	16 (10–27)	0.768
Histologic type, n (%)			0.151
– IDC	1010 (86.32%)	490 (83.76%)	
– Other	160 (13.68%)	95 (16.24%)	
Grade, n (%)			0.971
– I–II	817 (69.83%)	408 (69.74%)	
– III	353 (30.17%)	177 (30.26%)	
ER status, n (%)			0.397
– Negative	149 (12.74%)	83 (14.19%)	
– Positive	1021 (87.26%)	502 (85.81%)	
PR status, n (%)			0.306
– Negative	276 (23.59%)	151 (25.81%)	
– Positive	894 (76.41%)	434 (74.19%)	
HER2 status, n (%)			0.803
– Negative	1015 (86.75%)	510 (87.18%)	
– Positive	155 (13.25%)	75 (12.82%)	
Breast subtype, n (%)			0.733
– HR+/HER2-	904 (77.26%)	450 (76.92%)	
– HR+/HER2+	119 (10.17%)	53 (9.06%)	
– HR-/HER2+	36 (3.08%)	22 (3.76%)	
– HR-/HER2-	111 (9.49%)	60 (10.26%)	
Stage T, n (%)			0.188
– T1–T2	1110 (94.87%)	546 (93.33%)	
– T3–T4	60 (5.13%)	39 (6.67%)	
Stage N, n (%)			0.882
– N0	832 (71.11%)	414 (70.77%)	
– N1–N3	338 (28.89%)	171 (29.23%)	

Notes: All the bolded texts have no special meaning.
Abbreviations: IQR, interquartile range; mm, millimeter; IDC, invasive ductal carcinoma; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Regarding bone marrow micrometastasis, a study by Stephan Braun et al[10] found that, compared with female breast cancer patients without bone marrow micrometastasis, those with bone marrow micrometastases had larger tumor volumes, higher histologic grades, and higher rates of lymph node metastasis and hormone receptor–negative tumors, with all differences reaching statistical significance. Prognostically, bone marrow micrometastasis was independently associated with worse outcomes for both OS and BCSS. Similarly, previous studies[11,17,18] have shown that the presence of ITCs in the bone marrow is an independent predictor of distant disease–free survival, OS, and BCSS. A review by Stanley P. L. Leong et al[12] noted that patients with micrometastases—including ITCs and CTCs—in the bone marrow or peripheral blood have poorer clinical outcomes compared with patients without evidence of dissemination to these compartments.These findings differ somewhat from our results, as in our study, no statistically significant survival differences were observed between the M0(i+) and M0 groups. This discrepancy may be related to the broad definition of M0(i+). In addition, a prospective study indicated that in a cohort of early breast cancer patients with sentinel lymph node–negative status, bone marrow micrometastasis did not significantly affect 5-year disease-free survival or OS.[19] These results suggest that the impact of bone marrow micrometastases on breast cancer prognosis may be complex rather than a simple linear relationship. Importantly, in our study, the relatively high proportion of non–cancer-related deaths among early breast cancer patients may obscure the true prognostic value of bone marrow micrometastases when evaluated using OS.

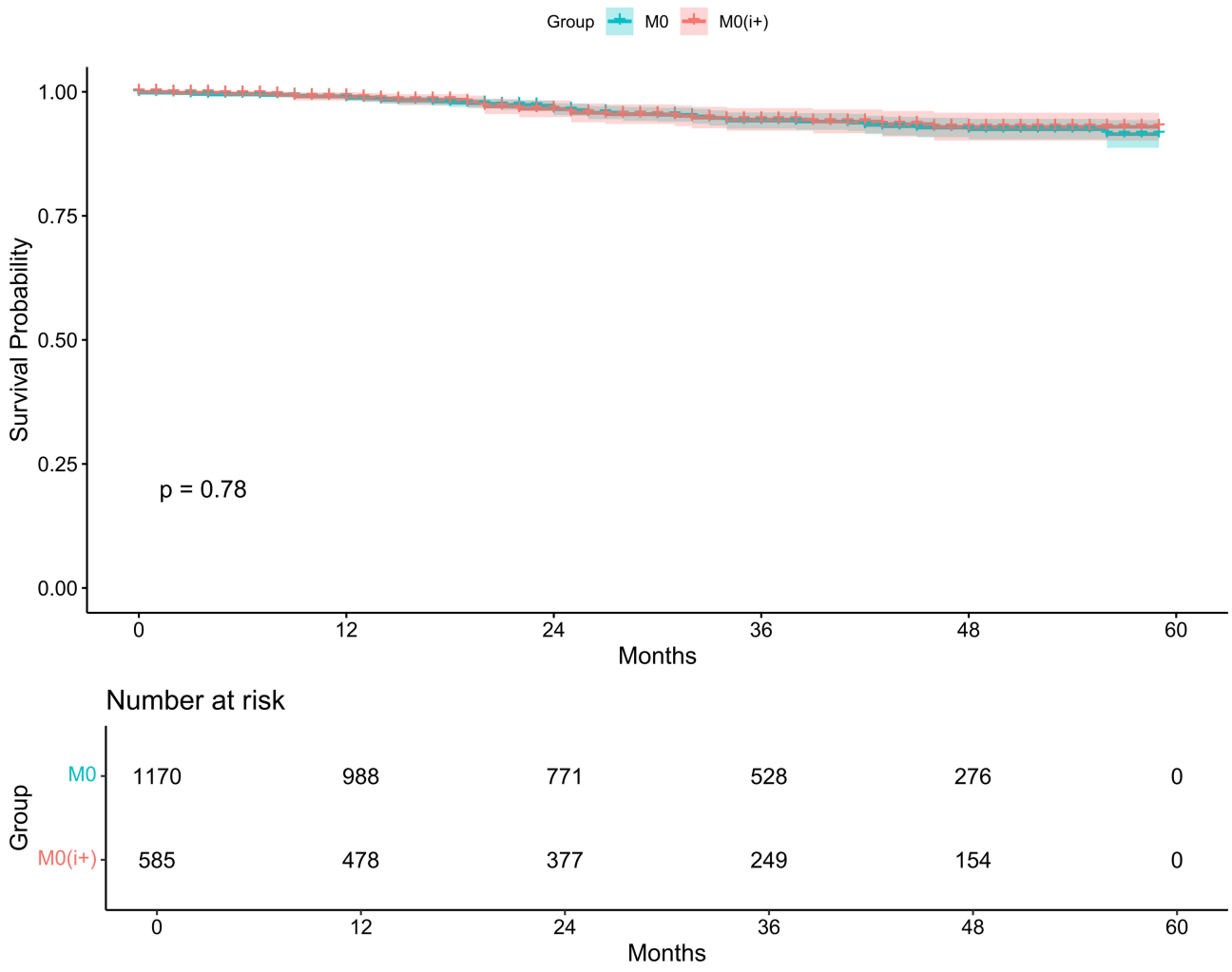

Figure 3 The survival curves of the M0 and M0(i+) groups after matching.

Based on these findings, we believe that future editions of the AJCC staging manual should further consider whether M0(i+) requires a more refined definition, such as separately categorizing micrometastases in the bone marrow, peripheral blood, and non-regional lymph nodes. Particular emphasis should be placed on the prognostic significance of bone marrow micrometastases and ITCs to more accurately reflect their potential impact on outcomes. Notably, the bone marrow serves as a common niche for disseminated tumor cells (DTCs) and CTCs.[20–22] Studies have shown that DTCs possess stem cell–like properties, enabling them to survive chemotherapy and remain in a dormant, non-proliferative state for years.[21] However, it is also important to note that bone marrow puncture is not a convenient procedure for patients. It needs to be performed under general anesthesia or local anesthesia and may pose challenges in practical applications. Peripheral blood CTCs are easier to obtain, but they cannot replace the results of DTC in bone marrow.[23] Furthermore, existing research on lymph node micrometastases has primarily focused on regional lymph nodes,[24–27] whereas evidence regarding non-regional lymph nodes remains limited and warrants further investigation.

Previous studies have confirmed that both bone marrow micrometastases and CTCs possess predictive value for treatment response. For example, Stephan Braun et al[10] reported that breast cancer patients with bone marrow micrometastases experienced significantly shorter BCSS when treated with endocrine therapy or cytotoxic chemotherapy. In addition, several studies have demonstrated a correlation between CTCs and treatment resistance in breast cancer.[28,29] In patients with metastatic breast cancer, specific CTC populations exhibit chemoresistance and can serve as predictors of poor prognosis.[30,31]

Table 3 Univariable and Multivariable Cox Proportional Hazards Analysis of Matched Cohort

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (per year)	1.069 (1.049–1.090)	**<0.001**	1.075 (1.055–1.096)	**<0.001**
Tumor size (mm)	1.029 (1.013–1.046)	**<0.001**	1.024 (1.014–1.034)	**<0.001**
Histologic type (Other vs IDC)	1.702 (0.943–3.072)	0.078	–	–
Grade (III vs I–II)	2.363 (1.311–4.258)	**0.004**	3.065 (1.959–4.797)	**<0.001**
ER positive vs negative	5.48×10^{5} (0–Inf)	0.996	–	–
PR positive vs negative	1.376 (0.609–3.108)	0.443	–	–
HER2 positive vs negative	9.29×10^{5} (0–Inf)	0.996	–	–
Breast subtype (HR+/HER2+ vs HR+/HER2–)	1.18×10^{-6} (0–Inf)	0.996	–	–
Breast subtype (HR–/HER2+ vs HR+/HER2–)	NA	NA	–	–
Breast subtype (HR–/HER2– vs HR+/HER2–)	1.60×10^{6} (0–Inf)	0.996	–	–
T stage (T3–T4 vs T1–T2)	0.524 (0.170–1.616)	0.261	–	–
N stage (N1–N3 vs N0)	1.722 (1.089–2.722)	**0.020**	1.672 (1.057–2.643)	**0.028**
Group (M0(i+) vs M0)	0.803 (0.498–1.296)	0.369	0.805 (0.501–1.294)	0.370

Notes: The bolded P values indicate significant statistical significance ($p < 0.05$), while the other bolded texts have no specific meaning.
Abbreviations: HR, Hazard ratio; CI, confidence interval; mm: millimeter; IDC, invasive ductal carcinoma; HR+, hormone receptor positive; HR, hormone receptor negative; HER2, human epidermal growth factor receptor 2; Inf, infinity.

Our study has several limitations. First, due to the limited number of M0(i+) patients in the SEER database and substantial missing data for treatment-related variables, we were unable to include specific treatment modalities in the analysis, which may introduce bias. Second, because M0(i+) cases were extremely rare in the database before 2018, our study only included patients diagnosed between 2018 and 2022. Consequently, the follow-up period was relatively short, leading to the presence of some extreme values. Third, as a retrospective study, inherent design limitations make it difficult to completely eliminate selection bias and residual confounding. Finally, our study was based on a US population, and the generalizability of the results to other countries and regions remains to be validated. Given these limitations, there is an urgent need for future multicenter, prospective studies with larger sample sizes and longer follow-

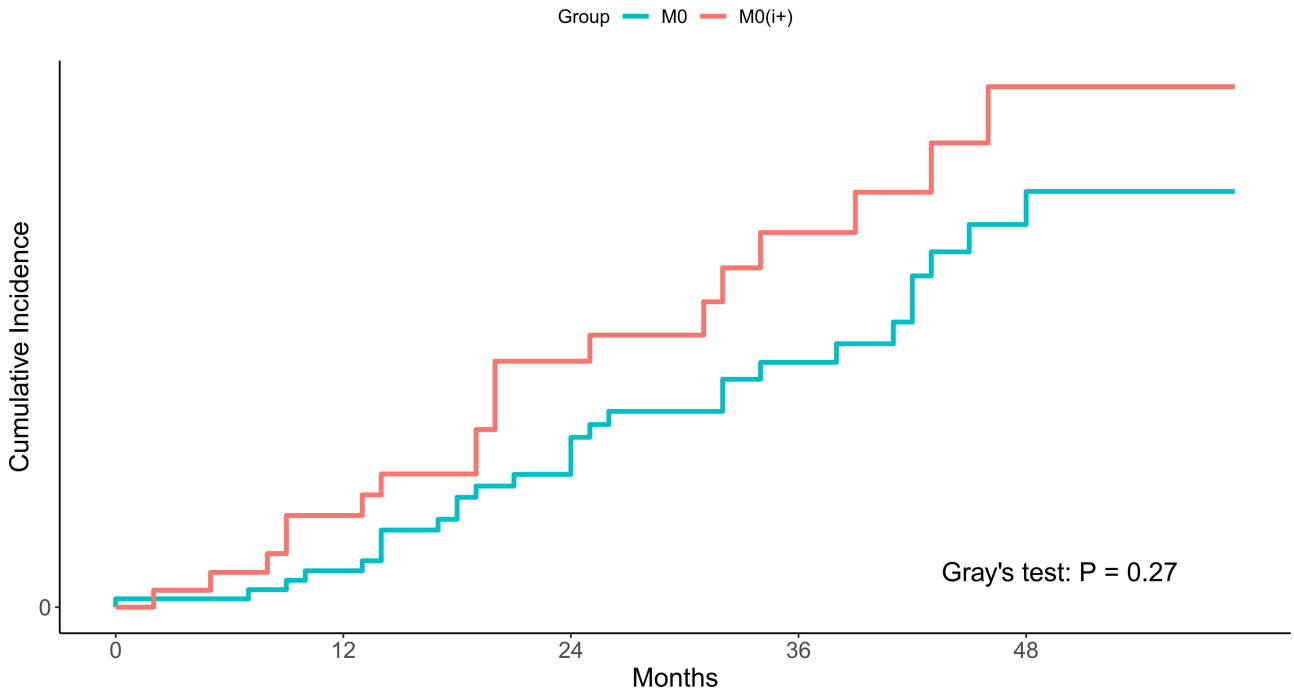

Figure 4 The cumulative incidence function curves of the M0 and M0(i+) groups after matching.

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Table 4 Univariable and Multivariable Competing Risk Regression Analysis of Matched Cohort

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (per year)	1.033 (1.003–1.063)	**0.029**	1.038 (1.012–1.070)	**0.003**
Tumor size (mm)	1.034 (1.024–1.044)	**<0.001**	1.042 (1.020–1.070)	**<0.001**
Histologic type (Other vs IDC)	1.304 (0.610–2.787)	0.493	—	—
Grade (III vs I–II)	3.833 (2.132–6.889)	**<0.001**	1.874 (0.850–4.130)	0.120
ER positive vs negative	0.189 (0.106–0.337)	**<0.001**	2.41×10^{3} ($493–1.18\times10^{4}$)	**<0.001**
PR positive vs negative	0.249 (0.140–0.442)	**<0.001**	0.701 (0.272–1.810)	0.460
HER2 positive vs negative	0.792 (0.312–2.005)	0.622	—	—
Breast subtype (HR+/HER2+ vs HR+/HER2–)	0.961 (0.290–3.188)	0.949	0.825 (0.222–3.060)	0.770
Breast subtype (HR–/HER2+ vs HR+/HER2–)	2.190 (0.509–9.421)	0.293	2.27×10^{3} ($253–2.04\times10^{4}$)	**<0.001**
Breast subtype (HR–/HER2– vs HR+/HER2–)	6.389 (3.468–11.769)	**<0.001**	5.64×10^{3} ($929–3.42\times10^{4}$)	**<0.001**
T stage (T3–T4 vs T1–T2)	3.572 (1.597–7.989)	**0.002**	0.291 (0.061–1.390)	0.120
N stage (N1–N3 vs N0)	2.702 (1.530–4.771)	**0.001**	2.170 (1.183–3.980)	**0.012**
Group (M0(i+) vs M0)	1.386 (0.775–2.480)	0.272	1.273 (0.679–2.390)	0.450

Notes: The bolded P values indicate significant statistical significance ($p < 0.05$), while the other bolded texts have no specific meaning.
Abbreviations: HR, Hazard ratio; CI, confidence interval; mm, millimeter; IDC, invasive ductal carcinoma; HR+, hormone receptor positive; HR, hormone receptor negative; HER2, human epidermal growth factor receptor 2.

up periods to comprehensively clarify the prognostic value of M0(i+) status and to further evaluate its potential role in guiding clinical treatment decisions.

Conclusion

This study indicates that OS and BCSM in M0(i+) breast cancer patients are comparable to those in M0 patients, supporting the rationale for combining M0(i+) with M0 in the AJCC staging system. Although survival differences did not reach statistical significance, M0(i+) may have potential adverse prognostic implications. Future studies should include large, multicenter, prospective cohorts with longer follow-up to comprehensively clarify the prognostic significance of the M0(i+) status and further evaluate its potential role in clinical decision-making. In light of previous studies, future editions of the AJCC staging manual may consider a more refined classification of M0(i+), particularly emphasizing the prognostic significance of bone marrow micrometastases, to more accurately reflect their impact on prognosis and guide treatment decisions.

Data Sharing Statement

The data used in this study are publicly available from the SEER program of the US National Cancer Institute. Researchers can access the data by applying for access at https://seer.cancer.gov. We warmly welcome potential collaborations. The data extraction rules, detailed study protocol, and R code can be obtained from the corresponding author, Song Tang (tangsong0802@163.com), upon reasonable request.

Ethical Approval

This study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (SYSKY-2025-835-01). The requirement for informed consent was waived. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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