

Temporal Trends in Survival Among Patients With De Novo Breast Cancer Liver Metastasis, 2010–2023: A Population-Based Cohort Study

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Abstract

Purpose: Liver metastasis at the time of breast cancer diagnosis represents a clinically challenging subgroup with historically poor prognosis. Although systemic therapies for metastatic breast cancer have evolved substantially, population-level survival trends among patients with de novo breast cancer liver metastasis (BCLM) remain incompletely characterized. We aimed to evaluate temporal changes in survival and assess whether survival improvements differed across clinical and social subgroups.

Methods: We identified patients with de novo BCLM diagnosed between 2010 and 2023 from the Surveillance, Epidemiology, and End Results (SEER) 17 Registries. Patients were categorized into four diagnostic eras (2010–2012, 2013–2016, 2017–2019, and 2020–2023). Overall survival was evaluated using multivariable Cox regression models, marginally standardized 24-month overall survival (S24), and 24-month restricted mean survival time (RMST24). Prespecified subgroup analyses examined interactions between diagnostic era and molecular subtype, metastatic burden, and social characteristics, with adjustment for multiple comparisons.

Results: Among 12,797 eligible patients, 10,870 with known molecular subtype comprised the primary analytic cohort. Adjusted S24 increased from 41.6% in 2010–2012 to 47.2% in 2020–2023, corresponding to an increase of 1.08 months in adjusted RMST24. However, compared with the 2017–2019 era, patients diagnosed in 2020–2023 showed no additional improvement in S24 (difference, –0.17 percentage points; 95% CI, –2.53 to 2.35) or RMST24 (difference, –0.03 months; 95% CI, –0.48 to 0.45). No statistically robust evidence of differential temporal survival changes was observed across molecular subtype, metastatic burden, race/ethnicity, marital status, neighborhood income, or rural–urban status after multiplicity adjustment.

Conclusions: Survival among patients with de novo BCLM improved during 2010–2023, although recent gains appeared limited. These findings provide a population-level assessment of contemporary survival patterns and highlight the need for continued efforts to improve outcomes for patients with liver metastatic breast cancer.

1. Introduction

Liver metastasis is one of the most clinically consequential manifestations of metastatic breast cancer and is associated with substantial mortality, particularly when present at the time of initial diagnosis.¹ Metastatic breast cancer represents the most advanced stage of disease and contributes substantially to cancer-related morbidity and mortality worldwide.^{2,3} Over the past decade, treatment strategies for advanced breast cancer have evolved toward increasingly subtype-directed approaches.⁴ In HER2-positive disease, dual HER2 blockade has produced substantial survival improvements⁵; in hormone receptor (HR)-positive/HER2-negative disease, cyclin-dependent kinase 4/6 inhibitors combined with endocrine therapy have become a central component of systemic treatment⁶; and in triple-negative

breast cancer (TNBC), immune checkpoint inhibitors and antibody–drug conjugates have expanded therapeutic options for selected patients⁷.

Population-based studies have demonstrated improving survival among patients with de novo stage IV breast cancer during the modern treatment era, suggesting that advances in systemic therapy have translated into broader clinical benefit.⁸ However, patients presenting specifically with de novo breast cancer liver metastasis (BCLM) represent a distinct clinical population with high metastatic burden and historically poor prognosis, and the extent to which recent therapeutic advances have improved survival in this subgroup remains uncertain.^{9–11} Furthermore, whether survival improvements have occurred uniformly across molecular subtypes, metastatic burden categories, and social groups has not been comprehensively evaluated.^{12,13}

Therefore, we conducted a population-based cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) 17 Registries to characterize temporal trends in survival among patients with de novo BCLM diagnosed from 2010 through 2023. We quantified changes in 24-month overall survival (S24) and restricted mean survival time (RMST24) across diagnostic eras and evaluated whether survival gains differed according to molecular subtype, metastatic burden, and social characteristics. These analyses aimed to define the magnitude, timing, and distribution of population-level survival changes in the contemporary era of metastatic breast cancer care.

2. Materials and Methods

2.1 Data Source and Study Population

We conducted a retrospective population-based cohort study using data from the SEER 17 Registries.¹⁴ The SEER database provides population-based information on cancer incidence, clinical characteristics, treatment receipt, and survival outcomes among patients diagnosed with malignancies in the United States. We identified patients diagnosed with de novo BCLM between 2010 and 2023. Eligible patients were those with breast cancer recorded as the primary malignancy and liver metastasis documented at the time of initial diagnosis. Patients were excluded according to prespecified eligibility criteria, including those without required survival information and those lacking key variables necessary for the primary analyses. The final eligible cohort included 12,797 patients. Because molecular subtype was required for the primary subgroup analyses, patients with known molecular subtype information (n = 10,870) comprised the primary analytic cohort. Patients with unknown molecular subtype were excluded from the primary analysis and were evaluated in sensitivity analyses using inverse probability of selection weighting.

2.2 Diagnostic Era Definition and Study Variables

Patients were categorized into four diagnostic eras according to year of diagnosis: 2010–2012, 2013–2016, 2017–2019, and 2020–2023. These periods were selected to characterize temporal changes in

survival during the contemporary era of metastatic breast cancer management. Prespecified covariates included age at diagnosis, breast cancer molecular subtype, metastatic burden, race/ethnicity, marital status, county-level median household income, and rural–urban status. Molecular subtype was classified as HR+/HER2–, HR+/HER2+, HR–/HER2+, and TNBC. Metastatic burden was categorized as liver-only metastasis, liver metastasis with one additional extrahepatic metastatic site, or liver metastasis with multiple extrahepatic metastatic sites. Social characteristics included race/ethnicity, marital status, county-level median household income, and rural–urban status, which were evaluated as potential effect modifiers in subgroup analyses.

2.3 Outcomes

The primary outcome was overall survival (OS), defined as the time from breast cancer diagnosis to death from any cause. To quantify clinically interpretable changes in survival across diagnostic eras, we estimated adjusted S24 and RMST24.¹⁵ S24 represents the estimated probability of surviving to 24 months after diagnosis, whereas RMST24 represents the average survival time accrued during the first 24 months after diagnosis. Breast cancer-specific survival (BCSS) and breast cancer-specific mortality were evaluated in sensitivity analyses. Competing risks of non–breast cancer death were considered using Fine–Gray models.

2.4 Statistical Analysis

Baseline characteristics were summarized across diagnostic eras using descriptive statistics. Continuous variables were summarized using appropriate measures of central tendency and dispersion, and categorical variables were presented as frequencies and proportions. Overall survival was analyzed using multivariable Cox proportional hazards regression models. The primary model (Model A) adjusted for age at diagnosis, molecular subtype, metastatic burden, race/ethnicity, marital status, county-level median household income, and rural–urban status. Because treatment receipt may represent an intermediate pathway through which temporal changes in clinical management influence survival, treatment variables were not included in the primary model. A secondary model (Model B) additionally adjusted for SEER-recorded chemotherapy, radiotherapy, and primary-site surgery to evaluate whether temporal survival differences remained after accounting for recorded treatment differences. Adjusted 24-month survival estimates were obtained using marginal standardization based on the regression models.¹⁶ Confidence intervals were calculated using bootstrap resampling. Differences in S24 and RMST24 between diagnostic eras were estimated with 95% confidence intervals.

2.5 Subgroup and Interaction Analyses

Prespecified subgroup analyses were performed to evaluate whether temporal changes in survival differed according to molecular subtype, metastatic burden, race/ethnicity, marital status, county-level median household income, and rural–urban status. Era-by-subgroup interactions were assessed using likelihood-ratio tests comparing models with and without interaction terms. Interaction analyses were conducted separately for Model A and Model B. To account for multiple comparisons, P values were adjusted using the Benjamini–Hochberg procedure across prespecified effect modifiers.¹⁷

2.6 Sensitivity Analyses

Several sensitivity analyses were performed to evaluate the robustness of the primary findings. First, analyses were repeated among patients diagnosed through 2021 to ensure complete potential 24-month follow-up for all patients. Second, breast cancer-specific survival analyses were performed using multivariable Cox regression. Third, competing-risk analyses for breast cancer-specific mortality were conducted using Fine–Gray proportional subdistribution hazards models.¹⁸ Fourth, inverse probability of selection weighting was applied to address potential selection bias associated with exclusion of patients with unknown molecular subtype. Additional sensitivity analyses evaluated whether adjustment for SEER-recorded treatment variables influenced subtype-specific survival trends and era-by-molecular subtype interactions.

2.7 Ethical Considerations and Data Availability

The SEER database contains deidentified cancer registry data. This study used publicly available, deidentified data and was conducted in accordance with applicable institutional and regulatory requirements. Data used in this study were obtained from the SEER database.

3. Results

3.1 Patient Characteristics

Among 12,797 eligible patients with de novo BCLM diagnosed between 2010 and 2023, 1,927 (15.1%) had unknown molecular subtype and were excluded from the primary known-subtype analyses. The resulting primary OS cohort comprised 10,870 patients, including 1,860 diagnosed in 2010–2012, 2,929 in 2013–2016, 2,456 in 2017–2019, and 3,625 in 2020–2023. For BCSS analyses, a further 97 patients with missing cause-specific survival information were excluded, leaving 10,773 patients. The cohort selection process is shown in Fig. 1.

Baseline demographic, tumor, metastatic, and SEER-recorded treatment characteristics according to diagnostic era are summarized in Table 1. The table describes the distribution of age, race/ethnicity, marital status, area-level income, rural–urban residence, molecular subtype, metastatic burden, chemotherapy, radiotherapy, and primary-site surgery across the four diagnostic eras. These characteristics were subsequently accounted for in the prespecified multivariable analyses as appropriate.

Table 1

Baseline characteristics of patients with de novo breast cancer liver metastasis by diagnostic era.

Variable	Characteristic	Overall	2010–2012	2013–2016	2017–2019	2020–2023	P value
Age at diagnosis	< 40 years	1129 (10.4%)	165 (8.9%)	317 (10.8%)	236 (9.6%)	411 (11.3%)	< 0.001
	40–49 years	1738 (16.0%)	330 (17.7%)	450 (15.4%)	393 (16.0%)	565 (15.6%)	
	50–64 years	4198 (38.6%)	785 (42.2%)	1186 (40.5%)	954 (38.8%)	1273 (35.1%)	
	65–74 years	2123 (19.5%)	315 (16.9%)	561 (19.2%)	472 (19.2%)	775 (21.4%)	
	≥ 75 years	1682 (15.5%)	265 (14.2%)	415 (14.2%)	401 (16.3%)	601 (16.6%)	
Race/ethnicity	NH White	6441 (59.3%)	1215 (65.3%)	1827 (62.4%)	1446 (58.9%)	1953 (53.9%)	< 0.001
	NH Black	1861 (17.1%)	306 (16.5%)	499 (17.0%)	398 (16.2%)	658 (18.2%)	
	Hispanic	1446 (13.3%)	187 (10.1%)	337 (11.5%)	337 (13.7%)	585 (16.1%)	
	NH API	1024 (9.4%)	136 (7.3%)	243 (8.3%)	254 (10.3%)	391 (10.8%)	
	Other/Unknown	98 (0.9%)	16 (0.9%)	23 (0.8%)	21 (0.9%)	38 (1.0%)	
Marital status	Married	4887 (45.0%)	845 (45.4%)	1310 (44.7%)	1102 (44.9%)	1630 (45.0%)	< 0.001
	Unmarried	5514 (50.7%)	907 (48.8%)	1457 (49.7%)	1248 (50.8%)	1902 (52.5%)	
	Unknown	469 (4.3%)	108 (5.8%)	162 (5.5%)	106 (4.3%)	93 (2.6%)	
County-level median household income	High	2995 (27.6%)	377 (20.3%)	663 (22.6%)	743 (30.3%)	1212 (33.4%)	< 0.001
	Upper-middle	3681 (33.9%)	476 (25.6%)	838 (28.6%)	939 (38.2%)	1428 (39.4%)	
	Lower-middle	2884 (26.5%)	745 (40.1%)	1000 (34.1%)	509 (20.7%)	630 (17.4%)	
	Low	1310 (12.1%)	262 (14.1%)	428 (14.6%)	265 (10.8%)	355 (9.8%)	

Variable	Characteristic	Overall	2010–2012	2013–2016	2017–2019	2020–2023	P value
Rural–urban status	Metropolitan	9721 (89.4%)	1662 (89.4%)	2595 (88.6%)	2204 (89.7%)	3260 (89.9%)	0.395
	Non-metropolitan	1133 (10.4%)	195 (10.5%)	328 (11.2%)	247 (10.1%)	363 (10.0%)	
	Unknown	16 (0.1%)	3 (0.2%)	6 (0.2%)	5 (0.2%)	2 (0.1%)	
Breast cancer subtype	HR+/HER2-	5004 (46.0%)	876 (47.1%)	1314 (44.9%)	1146 (46.7%)	1668 (46.0%)	0.013
	HR+/HER2+	2420 (22.3%)	432 (23.2%)	688 (23.5%)	553 (22.5%)	747 (20.6%)	
	HR-/HER2+	1760 (16.2%)	273 (14.7%)	504 (17.2%)	385 (15.7%)	598 (16.5%)	
	TNBC	1686 (15.5%)	279 (15.0%)	423 (14.4%)	372 (15.1%)	612 (16.9%)	
Metastatic burden	Liver-only	3081 (28.3%)	561 (30.2%)	804 (27.4%)	692 (28.2%)	1024 (28.2%)	0.049
	Liver + one extra-organ	4655 (42.8%)	794 (42.7%)	1278 (43.6%)	1085 (44.2%)	1498 (41.3%)	
	Liver + multiple extra-organs	3134 (28.8%)	505 (27.2%)	847 (28.9%)	679 (27.6%)	1103 (30.4%)	
SEER-recorded chemotherapy	No/Unknown	3369 (31.0%)	635 (34.1%)	974 (33.3%)	741 (30.2%)	1019 (28.1%)	< 0.001
	Yes	7501 (69.0%)	1225 (65.9%)	1955 (66.7%)	1715 (69.8%)	2606 (71.9%)	
SEER-recorded radiotherapy	No/Unknown	7811 (71.9%)	1315 (70.7%)	2089 (71.3%)	1764 (71.8%)	2643 (72.9%)	0.303
	Yes	3059 (28.1%)	545 (29.3%)	840 (28.7%)	692 (28.2%)	982 (27.1%)	
Primary-site surgery	No	7948 (73.1%)	1293 (69.5%)	2329 (79.5%)	2033 (82.8%)	2293 (63.3%)	< 0.001
	Yes	2922 (26.9%)	567 (30.5%)	600 (20.5%)	423 (17.2%)	1332 (36.7%)	

Data are presented as n (%). P values were calculated using the chi-square test and represent differences in variable distributions across diagnostic eras. SEER, Surveillance, Epidemiology, and End Results; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; NH, Non-Hispanic; API, Asian/Pacific Islander.

3.2 Overall survival improvement across diagnostic eras

Kaplan–Meier analysis showed significant differences in OS across diagnostic eras, with later eras generally demonstrating more favorable survival than 2010–2012 (log-rank $P < .001$; Fig. 2). After covariate adjustment and marginal standardization, the estimated S24 increased from 41.6% in 2010–2012 to 44.8% in 2013–2016, 47.3% in 2017–2019, and 47.2% in 2020–2023. Relative to 2010–2012, these estimates corresponded to absolute gains of 3.2, 5.7, and 5.5 percentage points, respectively. The corresponding RMST24 increased from 14.47 months in 2010–2012 to 15.10, 15.58, and 15.55 months in the three subsequent eras, representing gains of 0.63, 1.11, and 1.08 months, respectively (Table 2).

The largest cumulative improvement relative to 2010–2012 was observed by 2017–2019, whereas little additional gain was evident in the most recent era. In the direct comparison of 2020–2023 with 2017–2019, the adjusted S24 difference was -0.17 percentage points (95% CI, -2.53 to 2.35), and the RMST24 difference was -0.032 months (95% CI, -0.481 to 0.447). Thus, the grouped-era analysis indicated substantial improvement over the study period, with limited additional absolute gains after 2017–2019 and no clear evidence of further improvement in 2020–2023 (Table 2).

Table 2 Adjusted 24-month overall survival and restricted mean survival time across diagnostic eras.				
Diagnostic era or comparison	Adjusted 24-month OS, % (95% CI)	Absolute difference in 24-month OS, percentage points (95% CI)	Adjusted 24-month RMST, months (95% CI)	Difference in 24-month RMST, months (95% CI)
2010–2012	41.6 (39.8–43.6)	Reference	14.47 (14.10–14.86)	Reference
2013–2016	44.8 (43.2–46.5)	+ 3.2 (+ 0.8 to + 5.5)	15.10 (14.80–15.42)	+ 0.63 (+ 0.15 to + 1.09)
2017–2019	47.3 (45.4–49.1)	+ 5.7 (+ 3.1 to + 8.2)	15.58 (15.22–15.91)	+ 1.11 (+ 0.61 to + 1.60)
2020–2023	47.2 (45.5–48.8)	+ 5.5 (+ 3.0 to + 8.0)	15.55 (15.21–15.86)	+ 1.08 (+ 0.58 to + 1.56)
Direct contrast: 2020–2023 vs 2017–2019	—	-0.17 (-2.53 to + 2.35)	—	-0.03 (-0.48 to + 0.45)

RMST, restricted mean survival time; OS, overall survival; CI, confidence interval.

3.3 Heterogeneity in survival gains by molecular subtype and metastatic burden

We next evaluated whether the magnitude of era-associated survival improvement differed across prespecified clinical subgroups. In the primary Model A, there was no statistically significant evidence of heterogeneity by molecular subtype (P for interaction = .441; BH-adjusted P = .441) or metastatic burden (P for interaction = .297; BH-adjusted P = .441) after correction for multiple testing (Table 3). Thus, although subgroup-specific estimates differed numerically, the primary interaction analyses did not support differential temporal survival gains across molecular subtypes or levels of metastatic burden.

Subgroup-specific Cox estimates nevertheless showed generally lower mortality hazards in later diagnostic eras across most molecular subtype and metastatic-burden categories (Fig. 3). On the absolute scale, the adjusted S24 gain in 2020–2023 versus 2010–2012 was 4.2 percentage points for HR+/HER2 – disease, 9.3 percentage points for HR+/HER2 + disease, 3.1 percentage points for HR–/HER2 + disease, and 6.4 percentage points for TNBC. The corresponding RMST24 gains were 0.78, 1.64, 0.59, and 1.60 months, respectively. Across metastatic-burden groups, the S24 gains were 5.1 percentage points for liver-only disease, 3.1 percentage points for liver plus one extrahepatic organ, and 8.7 percentage points for liver plus multiple extrahepatic organs, with corresponding RMST24 gains of 0.90, 0.60, and 1.83 months. Complete subgroup-specific estimates across all diagnostic eras are provided in Supplementary Table S1.

Table 3
Era-by-subgroup interaction tests for heterogeneity in survival gains.

Effect modifier	N	Model A		Model B	
		Interaction P	BH-adjusted P	Interaction P	BH-adjusted P
Molecular subtype	10,870	0.441	0.441	< 0.001	< 0.001
Metastatic burden	10,870	0.297	0.441	0.276	0.331
Race/ethnicity	10,870	0.168	0.335	0.116	0.174
Marital status	10,870	0.404	0.441	0.335	0.335
Neighborhood income	10,870	0.125	0.335	0.108	0.174
Rural–urban status	10,854	0.029	0.171	0.042	0.127

3.4 Social heterogeneity and rural–urban patterns

We then examined whether temporal changes in OS varied across prespecified social subgroups. In the primary Model A, none of the social effect modifiers remained statistically significant after Benjamini–Hochberg correction for multiple testing (Table 3). The era-by-rural–urban interaction was nominally significant before correction (P for interaction = .029) but not after adjustment (BH-adjusted P = .171). Likewise, there was no multiplicity-adjusted evidence of heterogeneity by race/ethnicity, marital status,

or area-level income. These findings therefore did not support robust differences in temporal survival gains across the prespecified social subgroups.

Kaplan–Meier curves stratified by rural–urban residence were used to visualize era-specific survival patterns separately among metropolitan and non-metropolitan patients (Supplementary Figure S1). These curves were descriptive and were not used for formal inference regarding effect modification. In adjusted analyses, era-associated hazard ratios were estimated separately within metropolitan and non-metropolitan groups under the primary Model A (Supplementary Figure S2), while standardized S24 and RMST24 gains are reported in Supplementary Table S1. Taken together, the rural–urban-stratified analyses suggested differences in the visual pattern and magnitude of improvement across strata, but the formal interaction analysis did not provide multiplicity-adjusted evidence that temporal survival gains differed by rural–urban residence.

3.5 Robustness and sensitivity analyses

Several sensitivity analyses were conducted to evaluate the robustness of the primary findings under alternative analytic assumptions and outcome definitions. First, we restricted the cohort to patients diagnosed through 2021 to ensure complete potential 24-month follow-up for all included patients. In this restricted cohort, temporal patterns of OS remained consistent with the primary analysis, and extending follow-up completeness did not reveal additional recent-era survival gains (Supplementary Table S2). Furthermore, analyses using alternative survival endpoints yielded similar findings. BCSS demonstrated comparable era-associated patterns to OS (Supplementary Table S3), and Fine–Gray competing-risk analyses accounting for non-breast cancer mortality produced consistent estimates across diagnostic eras (Supplementary Table S4).

Because patients with unknown molecular subtype were excluded from the primary analytic cohort, we additionally evaluated the potential impact of subtype ascertainment bias using inverse probability of selection weighting (IPSW). Supplementary Table S5 summarizes subtype ascertainment patterns, standardized mean differences, IPSW diagnostics, comparisons of survival estimates before and after weighting, and IPSW-based analyses of era-associated survival heterogeneity. After IPSW adjustment, absolute survival estimates changed modestly, consistent with adjustment for differences between patients with known and unknown subtype; however, the magnitude and direction of era-associated survival gains and the conclusions regarding subgroup heterogeneity remained unchanged. These findings support the robustness of the primary results despite potential selection bias related to exclusion of patients with unknown molecular subtype.

3.6 Treatment-conditioned and exploratory treatment analyses

Because SEER-recorded treatment variables do not capture the complete complexity of contemporary breast cancer management, treatment-related analyses were considered exploratory and were interpreted as treatment-conditioned associations rather than causal explanations of survival changes.

We first evaluated whether adjustment for SEER-recorded treatments altered the observed temporal patterns of survival according to molecular subtype. In the primary Model A, the era-by-molecular-subtype interaction was not statistically significant, whereas the corresponding treatment-conditioned Model B showed a significant interaction (Supplementary Table S6). Sequential treatment adjustment further demonstrated that the largest change in the estimated subtype-specific interaction structure occurred after inclusion of SEER-recorded chemotherapy. These findings indicate that recorded treatment patterns were associated with changes in the treatment-conditioned model; however, they do not establish that chemotherapy explained or mediated survival heterogeneity. Molecular subtype-specific survival estimates after treatment adjustment are presented in Supplementary Figure S3, and temporal patterns of SEER-recorded chemotherapy receipt across molecular subtypes are shown in Supplementary Figure S4.

We next examined whether temporal changes in SEER-recorded chemotherapy, radiotherapy, and primary-site surgery differed across social groups. Across the 12 prespecified era-by-social-factor interaction tests, none remained statistically significant after Benjamini–Hochberg correction (Supplementary Table S7). Although some individual comparisons, including the low-income group and chemotherapy receipt, showed descriptive differences in the change of treatment recording over time, these findings were not interpreted as evidence of robust temporal treatment inequity.

Finally, we evaluated the overall associations of social factors with SEER-recorded treatment receipt and survival outcomes. Several social characteristics were associated with recorded treatment receipt and prognosis in multivariable analyses; however, these associations did not translate into robust evidence of differential temporal survival gains after formal interaction testing (Supplementary Table S8). These analyses were intended to characterize socially patterned differences in recorded treatment and outcomes and were distinguished from the primary analyses evaluating era-associated survival heterogeneity.

3.7 Annual trend in adjusted 24-month survival

To further characterize the temporal pattern of survival improvement beyond grouped diagnostic eras, we performed an annual trend analysis of adjusted S24 among patients diagnosed from 2010 through 2021. The annual adjusted S24 estimates and segmented log-linear generalized least squares models are summarized in Supplementary Table S9. Across the study period, adjusted S24 increased at an average annual rate of 1.28% per year (APC/AAPC, + 1.28%; 95% CI, 0.59 to 1.96; $P = .002$). Model selection based on both BIC and BIC3 favored the model without change points, indicating no evidence of a discrete inflection point in the annual survival trajectory. These findings complement the grouped-era analyses: although era-based comparisons suggested limited additional absolute survival gains in the most recent period, the annual trend analysis did not support a discrete change point and instead indicated a gradual improvement in adjusted S24 over time.

Discussion

In this population-based cohort study of patients with de novo BCLM, we observed measurable improvements in survival during the period from 2010 through 2023. Adjusted 24-month overall survival increased from 41.6% among patients diagnosed in 2010–2012 to 47.2% among those diagnosed in 2020–2023, corresponding to a gain of 1.08 months in adjusted 24-month restricted mean survival time. However, the magnitude of improvement varied across diagnostic periods. Compared with the 2017–2019 diagnostic era, patients diagnosed in 2020–2023 did not demonstrate additional improvement in either 24-month overall survival or restricted mean survival time. Furthermore, we found no consistent evidence of differential temporal survival changes across prespecified molecular, metastatic burden, or social subgroups after adjustment for multiple comparisons.

Previous population-based studies have demonstrated improving outcomes among patients with de novo stage IV breast cancer during the era of increasingly effective systemic therapies.^{8,19–21} Our findings extend this literature by focusing specifically on patients presenting with liver metastasis at the time of breast cancer diagnosis, a clinically distinct subgroup with substantial metastatic burden and historically unfavorable prognosis.²² Although advances in HER2-directed therapy, endocrine-based targeted approaches, immunotherapy, and antibody–drug conjugates have expanded treatment options for metastatic breast cancer, their population-level impact among patients with BCLM has remained incompletely characterized.^{10,23–25} Our findings suggest that the benefits associated with the modern treatment era have translated into measurable survival improvement at the population level among patients with BCLM. However, the lack of additional improvement observed in the most recent diagnostic era highlights the continued challenges in achieving further survival gains among patients with BCLM. This pattern highlights that continued advances in metastatic breast cancer care may require not only broader implementation of existing therapies but also strategies addressing treatment resistance, disease biology, and the clinical complexity associated with liver metastatic involvement.²⁶

An important objective of this study was to determine whether survival improvements were distributed consistently across clinically and socially defined subgroups. In the primary analysis, we found no statistically robust evidence that temporal survival improvements differed according to molecular subtype, metastatic burden, race and ethnicity, marital status, neighborhood income, or rural–urban status after multiplicity adjustment. These findings should be interpreted as the absence of detectable differential temporal changes rather than evidence that all groups experienced identical outcomes. Persistent survival differences according to baseline social and clinical characteristics may remain, as previously reported in metastatic breast cancer populations.²⁷ However, the magnitude of survival improvement over time did not differ consistently across the evaluated subgroups. The observed lack of significant heterogeneity may reflect broad dissemination of advances in metastatic breast cancer management, although the SEER database does not capture detailed information on treatment selection, treatment sequencing, adherence, or access to specific novel therapies. Further studies incorporating longitudinal treatment data are needed to better characterize mechanisms underlying temporal changes in survival disparities.

Molecular subtype is a major determinant of treatment selection and prognosis in metastatic breast cancer.²⁸ The relationship between molecular subtype and temporal survival changes warrants careful interpretation. In the primary model, no significant era-by-molecular subtype interaction was observed after adjustment for baseline clinical characteristics. However, after additional adjustment for SEER-recorded treatment variables, the interaction became statistically significant, suggesting that treatment-related factors may contribute to differences in observed survival trajectories across molecular subtypes. Because treatment variables may lie on the causal pathway between therapeutic advances and survival outcomes, these analyses should not be interpreted as demonstrating that treatment adjustment fully explains subtype-specific survival differences. Rather, the comparison between models provides insight into how recorded treatment patterns may influence observed population-level survival trends.²⁹

This study has several strengths. First, the large population-based cohort enabled evaluation of temporal survival patterns in a relatively uncommon but clinically important metastatic subgroup. Second, the use of marginally standardized survival estimates and RMST allowed assessment of absolute survival differences that may be more clinically interpretable than relative measures alone. Third, prespecified subgroup analyses and multiple sensitivity analyses strengthened the robustness of the findings. Several limitations should be acknowledged. First, as an observational registry-based study, causal relationships between therapeutic advances and survival improvement cannot be established. Second, SEER provides limited information on systemic therapy details, including specific agents, treatment sequencing, duration, and response, preventing direct attribution of survival changes to individual treatments. Third, potential residual confounding from unmeasured clinical factors, including performance status and comorbidity burden, remains possible. Fourth, patients diagnosed in the most recent years had shorter available follow-up, although sensitivity analyses restricted to patients with complete potential 24-month follow-up yielded similar results.

Conclusion

In conclusion, survival among patients with de novo breast cancer liver metastasis improved from 2010 through 2023, although the magnitude of improvement differed across diagnostic periods. No consistent evidence of differential temporal survival changes was observed across major clinical and social subgroups. These findings provide a population-level assessment of contemporary survival patterns in BCLM and highlight the need for continued efforts to improve outcomes for patients with liver metastatic breast cancer.

Declarations

Funding: This study received no external funding.

Conflict of interest: The authors declare that they have no conflict of interest.

Data Availability: The data used in this study were obtained from the SEER database and are publicly available.

Ethics approval and consent to participate: Not applicable.

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