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Sociodemographic and Facility-Level Determinants of HER2-Targeted Therapy Use in Metastatic HR−/HER2+ Breast Cancer

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ABSTRACT

Targeted inhibition of HER2 has transformed the management of metastatic hormone receptor–negative, HER2-positive (HR−/HER2+) breast cancer and substantially extended survival. Despite these advances, real-world patterns of treatment delivery and the factors shaping access to HER2-directed therapies are incompletely characterized. This study investigates patient-, social-, and facility-level characteristics associated with the receipt of HER2-targeted therapy in metastatic HR−/HER2+ breast cancer. Using the National Cancer Database, we identified patients diagnosed with metastatic HR−/HER2+ breast cancer between 2013 and 2020. Individuals were grouped according to whether they received HER2-targeted therapy, with exclusion of cases missing essential covariates. The study period was divided into three eras (pre-2015, 2016–2018, and 2019–2020) to reflect changes in therapeutic availability and clinical practice in the United States. Logistic regression analyses were performed to determine factors independently associated with treatment receipt. Overall survival was analyzed using Kaplan–Meier methods, log-rank testing, and Cox proportional hazards models. Among 3,060 eligible patients, 2,318 (75.8%) received HER2-targeted therapy. Treatment adoption increased sharply early in the study period, rising from 64.6% in 2013 to 80.9% by 2016, after which utilization plateaued and modestly declined, stabilizing near 75% during 2019–2020. More recent year of diagnosis, private insurance coverage, and care at academic institutions were independently associated with higher odds of receiving HER2-targeted therapy. In contrast, advanced age (≥71 years), Black race, Medicare insurance, and treatment at rural facilities were linked to lower treatment likelihood. Patients treated with HER2-targeted therapy experienced markedly superior outcomes, with substantially longer median survival (5.08 vs. 1.27 years) and a significantly reduced risk of death. Although HER2-targeted therapies are now widely incorporated into the treatment of metastatic HR−/HER2+ breast cancer, meaningful inequities in their use persist. Disparities related to age, race, insurance status, and treatment setting continue to influence access to these life-prolonging therapies. Efforts to reduce structural and systemic barriers are essential to ensure equitable treatment delivery and optimize outcomes across all patient populations.

Keywords: Treatment disparities, Metastatic HER2+/HR− breast cancer, HER2-targeted therapy, Survival outcomes.

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Introduction

Metastatic hormone receptor–negative, HER2-positive (HR−/HER2+) breast cancer constitutes a biologically aggressive form of metastatic breast cancer (MBC) that is associated with rapid disease progression and limited therapeutic durability [1]. Patients with this subtype frequently experience early treatment resistance and poor clinical outcomes, making disease management particularly challenging [2-4]. The development of therapies targeting the HER2 receptor has substantially altered the prognosis of HER2-positive breast cancer, including in the metastatic setting. Agents such as trastuzumab and pertuzumab have demonstrated meaningful survival benefits and are now central components of systemic therapy for metastatic disease [5-7]. However, despite their

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established efficacy, the real-world delivery of HER2-targeted therapies among patients with metastatic HR−/HER2+ breast cancer is not uniform, and determinants of access remain insufficiently characterized.

Prior research in metastatic breast cancer has demonstrated that treatment receipt is influenced by a complex interplay of patient characteristics and healthcare system factors. Sociodemographic variables, including age, race, and socioeconomic status, have been shown to affect the likelihood of receiving timely systemic therapy. For example, Pearson *et al*. reported higher rates of chemotherapy utilization among younger patients, White patients, and those with greater socioeconomic resources [8]. The type of treatment facility has also been shown to influence care delivery, with academic, research-focused, and private institutions more frequently associated with timely initiation of therapy [8]. In addition, Morimoto *et al*. identified clinical characteristics—such as lower comorbidity burden, greater disease severity, and hormone receptor–negative status—as predictors of chemotherapy use in metastatic breast cancer [9]. Geographic variation further contributes to treatment differences, as demonstrated by Caswell-Jin *et al*., who found that regional income levels and location significantly shaped treatment strategies, reflecting variability in local practice patterns and resource availability [10].

Although disparities in the management of metastatic breast cancer are increasingly recognized, studies specifically evaluating the use of HER2-directed therapies in metastatic HR−/HER2+ disease remain limited. The National Cancer Database (NCDB) provides a large, nationally representative dataset containing detailed clinical, demographic, and institutional information, offering a valuable platform to examine real-world treatment patterns and disparities [11-14]. Over the last decade, the therapeutic landscape for metastatic HER2-positive breast cancer has continued to evolve with the introduction of novel HER2-targeted agents [15, 16]. In particular, the approval of tucatinib in 2019 and trastuzumab deruxtecan in 2020 expanded available treatment options during the latter portion of the study period and further influenced clinical practice patterns [17-19]. Evaluating NCDB data across this interval allows for assessment of temporal changes in therapy utilization, identification of factors associated with treatment selection, and examination of survival outcomes in routine clinical practice.

The purpose of this study is to examine patient-level, sociodemographic, and facility-related factors associated with receipt of HER2-targeted therapy among individuals with metastatic HR−/HER2+ breast cancer. Using NCDB data, we aim to characterize trends in treatment use over time, identify disparities in access to HER2-directed therapies, and assess the association between therapy receipt and overall survival. These findings are intended to inform strategies aimed at improving equity in cancer care delivery and optimizing outcomes for patients with this aggressive breast cancer subtype.

Materials and Methods

Study design and data source

A retrospective cohort analysis was performed using the National Cancer Database (NCDB) to identify patients diagnosed with metastatic HR−/HER2+ breast cancer between 1 January 2013 and 31 December 2020. Treatment exposure was determined based on NCDB treatment coding, and patients were classified according to whether they received HER2-targeted systemic therapy. Cases lacking essential clinical, sociodemographic, or facility-level data were excluded to ensure analytic completeness.

During the study interval, HER2-directed agents such as trastuzumab and pertuzumab represented standard first-line therapy for metastatic HER2-positive breast cancer [18]. Subsequent regulatory approvals expanded available therapeutic options, including the introduction of tucatinib in 2019 for use in combination regimens and trastuzumab deruxtecan in 2020, which broadened treatment strategies during the later years of the study period [18].

To maintain a clinically uniform cohort, patients with hormone receptor–positive, HER2-positive (HR+/HER2+) breast cancer were excluded, as the management of HR+ disease differs substantially and often incorporates endocrine-based treatment approaches that may influence the use and sequencing of HER2-targeted therapies.

Description of the study population and group-level comparisons

The study cohort was divided according to exposure to HER2-directed systemic therapy, and characteristics were evaluated across these groups to identify differences in patient composition and care delivery. Variables of interest spanned demographic factors (including age, race, and ethnicity), healthcare system characteristics (such as type of treating institution, geographic setting, and whether care was received at more than one facility), and

socioeconomic context based on residential zip code–level indicators of income and educational attainment. Clinical features assessed included comorbidity burden using the Charlson Comorbidity Index, patterns of metastatic spread, receipt of additional cancer-directed treatments, and the calendar year in which the metastatic diagnosis was established.

Statistical methods

Analyses were performed to determine which patient, disease, and healthcare system factors were associated with receipt of HER2-targeted therapy. Initial exploratory analyses assessed individual associations between covariates and treatment status. Subsequently, multivariable logistic regression modeling was used to estimate adjusted associations, incorporating demographic characteristics, insurance coverage, facility-related variables, measures of urbanicity, neighborhood socioeconomic indicators, comorbidity burden, metastatic site involvement, multi-institutional care, concomitant therapies, and year of diagnosis.

Differences in categorical variables were evaluated using appropriate nonparametric tests, while continuous variables were compared using parametric methods. Overall survival was assessed by estimating survival distributions for treated and untreated patients using Kaplan–Meier techniques, with statistical comparisons performed using the log-rank test. Multivariable Cox proportional hazards models were then constructed to quantify the relationship between HER2-targeted therapy exposure and mortality while adjusting for relevant clinical, sociodemographic, and institutional confounders.

All statistical computations were conducted using RStudio software (Version 2023.12.0 + 369). A two-sided significance level of 0.05 was applied for all hypothesis testing.

Results and Discussion

Changes in HER2-targeted therapy use over time

Evaluation of treatment patterns revealed a pronounced increase in the use of HER2-targeted therapy among patients with metastatic HR−/HER2+ breast cancer during the early years of the study period. The proportion of patients receiving HER2-directed treatment rose from 64.6% in 2013 to 80.9% by 2016 **(Figure 1)**, ($p < 0.001$), indicating rapid early uptake. Although utilization declined modestly thereafter, treatment rates remained consistently high, leveling off at approximately 75.1% by 2020. Overall, these findings demonstrate sustained incorporation of HER2-targeted therapies into routine care across the study interval.

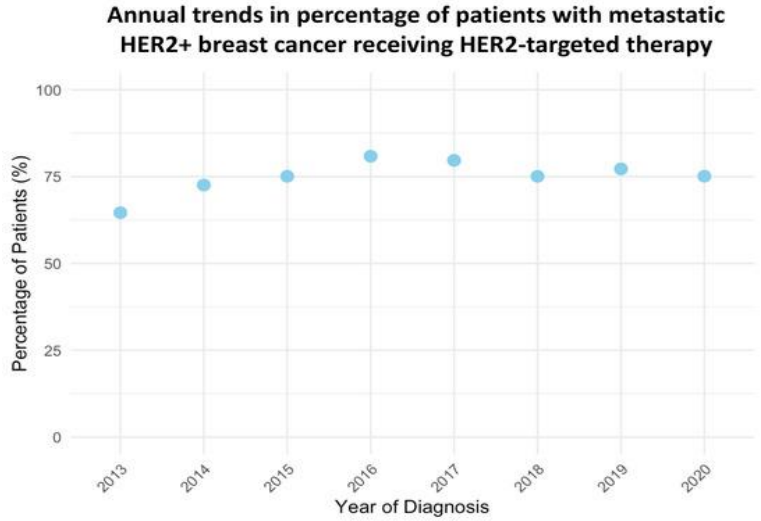

Figure 1. Year-by-year patterns in the administration of HER2-directed therapies among patients with metastatic HR−/HER2+ breast cancer between 2013 and 2020, demonstrating a statistically significant temporal trend ($p < 0.001$ based on linear trend analysis).

Patient demographics and treatment facility profiles

Using NCDB data, we identified 3,060 individuals diagnosed with metastatic HER2-positive breast cancer during the study period spanning 2013 to 2020. Within this cohort, 2,318 patients (75.8%) were treated with HER2-

targeted therapies, whereas 742 patients (24.2%) did not receive HER2-directed treatment. Baseline demographic characteristics, clinical features, socioeconomic indicators, and facility-level attributes of the study population, stratified by receipt of HER2-targeted therapy, are summarized in **Table 1.**

Table 1. Distribution of clinical, demographic, healthcare and socioeconomic facility characteristics among patients with metastatic HER2-positive breast cancer, according to receipt of HER2-targeted therapy.

Characteristic	Received HER2-Directed Therapy(N = 2318)	No HER2-Directed Therapy(N = 742)	p-Value
Age category			<0.001
40–54 years	789 (34.0%)	146 (19.6%)	
55–70 years	1132 (48.8%)	332 (44.5%)	
≥71 years	397 (17.1%)	268 (35.9%)	
Race			0.041
Black	385 (16.6%)	151 (20.2%)	
White	1784 (77.0%)	545 (73.1%)	
South Asian	82 (3.5%)	25 (3.4%)	
Asian	42 (1.8%)	12 (1.6%)	
Unknown	11 (0.5%)	9 (1.2%)	
Other	14 (0.6%)	4 (0.5%)	
Year at diagnosis			<0.001
2013–2015	608 (26.2%)	247 (33.1%)	
2016–2018	960 (41.4%)	264 (35.4%)	
2019–2020	750 (32.3%)	235 (31.5%)	
Type of treating facility			<0.001
Comprehensive cancer center	835 (36.0%)	301 (40.3%)	
Community cancer program	167 (7.2%)	90 (12.1%)	
Integrated network	476 (20.5%)	159 (21.3%)	
Academic center	840 (36.2%)	196 (26.3%)	
Hispanic or Spanish origin			0.004
No	2140 (92.3%)	677 (90.8%)	
Yes	148 (6.4%)	46 (6.2%)	
Unknown	30 (1.3%)	23 (3.1%)	
Care delivered at more than one CoC-accredited facility			<0.001
No	1841 (79.4%)	655 (87.8%)	
Yes	477 (20.6%)	91 (12.2%)	
Geographic setting			0.541
Rural	103 (4.4%)	27 (3.6%)	
Metropolitan	1909 (82.4%)	614 (82.3%)	
Urban	306 (13.2%)	105 (14.1%)	
Primary insurance coverage			<0.001
Private insurance	1130 (48.7%)	211 (28.3%)	
Uninsured	100 (4.3%)	37 (5.0%)	
Medicare	719 (31.0%)	384 (51.5%)	
Medicaid	325 (14.0%)	91 (12.2%)	
Other government plans	27 (1.2%)	7 (0.9%)	
Unknown	17 (0.7%)	16 (2.1%)	
Charlson Comorbidity Index			<0.001
0	1954 (84.3%)	559 (74.9%)	
1	264 (11.4%)	112 (15.0%)	
2	65 (2.8%)	36 (4.8%)	
≥3	35 (1.5%)	39 (5.2%)	
Median household income (zip code level)			<0.001
< USD 30,000	226 (9.7%)	135 (18.1%)	
USD 30,000–34,999	306 (13.2%)	99 (13.3%)	

USD 35,000–45,999	529 (22.8%)	143 (19.2%)	
≥ USD 46,000	887 (38.3%)	252 (33.8%)	
Unknown	370 (15.9%)	117 (15.7%)	
Additional cancer-directed treatments			
Surgery of the primary tumor	589 (25.4%)	98 (13.1%)	<0.001
Chemotherapy	2008 (86.6%)	282 (37.8%)	<0.001
Sites of metastatic disease			
Brain	118 (5.1%)	71 (9.5%)	<0.001
Bone	998 (43.0%)	301 (40.3%)	0.208
Lung	526 (22.7%)	190 (25.4%)	0.131
Liver	652 (28.1%)	188 (25.2%)	0.130
Other	190 (8.2%)	100 (13.4%)	<0.001

Patients treated with HER2-directed agents differed markedly from untreated patients across demographic, socioeconomic, clinical, and care-delivery domains. Age distribution showed a clear shift toward younger populations among therapy recipients. Individuals aged 40–54 and 55–70 years accounted for a larger share of treated patients, whereas those aged 71 years or older were disproportionately represented among patients who did not receive HER2-targeted therapy ($p < 0.001$ for all comparisons). Temporal trends also indicated increasing adoption of HER2-targeted treatments, with patients diagnosed after 2015 substantially more likely to receive therapy than those diagnosed earlier.

Variations by race and ethnicity were evident. White patients constituted a greater proportion of those receiving HER2-targeted therapy, while Black patients were less frequently treated ($p = 0.041$). Hispanic ethnicity was modestly but significantly more prevalent among treated patients ($p = 0.004$). Insurance coverage patterns differed strikingly between groups. Private insurance coverage was far more common among patients receiving HER2-targeted therapy, whereas Medicare coverage predominated among those who did not receive targeted treatment. Uninsured status was also slightly more frequent in the untreated group ($p < 0.001$ for all insurance comparisons). Socioeconomic status followed a similar gradient, with patients from higher-income areas more likely to receive HER2-directed therapy and those from lower-income regions more often untreated.

Access to specialized care appeared to influence treatment receipt. Patients receiving HER2-targeted therapy were more frequently managed at academic institutions and comprehensive cancer centers, while community-based facilities treated a higher proportion of patients who did not receive HER2-directed agents. Treatment across multiple Commission on Cancer–accredited facilities was also more common among therapy recipients, suggesting greater care complexity or referral patterns.

Clinical profiles further distinguished treated and untreated patients. Lower comorbidity burden was strongly associated with receipt of HER2-targeted therapy, with treated patients more often having no documented comorbid conditions and less frequently exhibiting high Charlson Comorbidity Index scores. Patterns of metastatic disease differed selectively: brain metastases were observed more often in patients who did not receive HER2-targeted therapy, whereas rates of bone, liver, and lung involvement were comparable between groups. Concomitant cancer-directed interventions varied substantially, as patients treated with HER2-targeted therapy were far more likely to receive systemic chemotherapy and to undergo surgical management of the primary tumor.

Predictors of HER2-targeted therapy use

Multivariable modeling identified several independent determinants of HER2-targeted therapy utilization. Age remained a dominant predictor after adjustment for covariates. Compared with patients aged 40–54 years, those aged 71 years or older demonstrated a markedly reduced likelihood of receiving HER2-directed therapy, while patients aged 55–70 years also showed lower odds, though to a lesser extent.

Year of diagnosis was strongly associated with treatment receipt. Patients diagnosed during 2016–2018 and 2019–2020 had nearly double the odds of receiving HER2-targeted therapy relative to those diagnosed between 2013 and 2015, reflecting evolving treatment standards and expanding availability of HER2-directed agents over time.

Table 2. Multivariable logistic regression evaluating predictors of HER2-targeted therapy receipt among patients with metastatic HER2-positive breast cancer

Variable	OR (95% CI)	p-value
Diagnosis period		

2013–2015	Reference	—
2016–2018	1.93 (1.40–2.65)	<0.001
2019–2020	1.88 (1.35–2.62)	<0.001
Age category		
40–54	Reference	—
55–70	0.76 (0.60–0.96)	0.025
≥71	0.41 (0.30–0.57)	<0.001
Hispanic/Spanish origin		
No	Reference	—
Yes	0.77 (0.51–1.17)	0.222
Race		
White	Reference	—
Black	0.81 (0.67–0.95)	0.043
South Asian	0.85 (0.22–3.27)	0.817
Asian	0.92 (0.44–1.94)	0.831
Other	0.91 (0.53–1.59)	0.751
Facility location		
Metropolitan	Reference	—
Urban	1.13 (0.83–1.53)	0.455
Rural	1.30 (0.77–2.19)	0.326
Facility classification		
Community	Reference	—
Comprehensive	1.47 (1.03–2.10)	0.035
Network	1.73 (1.17–2.56)	0.005
Academic	2.57 (1.77–3.73)	<0.001
Area-level median income		
< USD 30,000	Reference	—
USD 30,000–34,999	1.75 (1.19–2.56)	0.004
USD 35,000–45,999	1.65 (1.11–2.47)	0.004
≥ USD 46,000	1.78 (1.24–2.76)	0.010
Insurance coverage		
Uninsured	Reference	—
Private	1.79 (1.17–2.73)	0.007
Medicare	0.96 (0.57–1.62)	0.884
Medicaid	1.26 (0.74–2.15)	0.393
Other government	1.09 (0.36–3.35)	0.875
Care at multiple CoC facilities		
No	Reference	—
Yes	1.46 (1.10–1.94)	0.008
Charlson comorbidity score		
0	Reference	—
1	0.84 (0.63–1.13)	0.247
2	1.07 (0.65–1.75)	0.799
≥3	0.40 (0.22–0.73)	0.002
Additional treatments		
Chemotherapy	9.53 (7.65–11.86)	<0.001
Surgery at primary tumor	1.28 (0.97–1.68)	0.083
Metastatic involvement		
Brain	0.43 (0.29–0.64)	<0.001
Bone	0.99 (0.78–1.28)	0.976
Lung	1.00 (0.77–1.29)	0.992
Liver	0.98 (0.76–1.26)	0.876
Other sites	0.46 (0.27–0.89)	0.008

Determinants of HER2-directed treatment allocation

Multivariable analysis demonstrated that receipt of HER2-directed therapy was unevenly distributed across patient populations and care settings. Disparities related to race were evident, as Black patients showed significantly lower adjusted odds of receiving HER2-targeted treatment when compared with White patients (OR = 0.81, 95% CI: 0.67–0.95, p = 0.043), indicating persistent inequities in treatment delivery.

Access to HER2-directed therapy was also strongly influenced by financial and insurance-related factors. Patients covered by private insurance plans were substantially more likely to receive HER2-targeted agents than those without insurance (OR = 1.79, 95% CI: 1.17–2.73, p = 0.007). In parallel, neighborhood-level income demonstrated a consistent association with treatment utilization. Relative to individuals residing in areas with median household incomes below USD 30,000, patients from higher-income regions exhibited greater likelihood of HER2 therapy use, including those in the USD 30,000–34,999 (OR = 1.75, p = 0.004), USD 35,000–45,999 (OR = 1.65, p = 0.004), and ≥USD 46,000 (OR = 1.78, p = 0.010) income categories.

The healthcare environment in which patients received care further influenced treatment patterns. Compared with community-based facilities, treatment at academic centers was associated with the greatest increase in HER2-targeted therapy use (OR = 2.57, p < 0.001). Patients managed at comprehensive cancer centers and network-affiliated institutions also demonstrated higher odds of receiving HER2-directed treatment than those treated in community settings (OR = 1.47, p = 0.035; OR = 1.73, p = 0.005, respectively), suggesting that institutional specialization and infrastructure play a critical role in therapy adoption.

Clinical characteristics were additionally associated with treatment decisions. Patients with documented brain metastases were significantly less likely to receive HER2-targeted therapy (OR = 0.43, p < 0.001), potentially reflecting clinical complexity or perceived treatment limitations. Conversely, concurrent administration of systemic chemotherapy was the strongest predictor of HER2 therapy use (OR = 9.53, p < 0.001), highlighting the close integration of HER2-directed agents within combination treatment regimens. Surgical management of the primary tumor did not independently predict HER2 therapy receipt (OR = 1.28, p = 0.083). Furthermore, higher comorbidity burden adversely affected treatment allocation, as patients with a Charlson Comorbidity Index score of three or greater were markedly less likely to receive HER2-targeted therapy compared with patients without comorbid conditions (OR = 0.40, p = 0.002).

Survival differences according to HER2-targeted therapy use

A substantial survival advantage was observed among patients treated with HER2-directed therapies. Kaplan–Meier survival estimates demonstrated a pronounced separation between treatment groups **(Figure 2)**, with HER2-targeted therapy use associated with significantly improved overall survival (p < 0.001). Patients who did not receive HER2-targeted treatment experienced a median survival of 1.27 years (95% CI: 0.97–1.82). In contrast, those who received HER2-directed agents achieved a median overall survival exceeding five years (5.08 years; 95% CI: 4.25–6.03), underscoring the critical impact of access to HER2-targeted therapies on long-term outcomes.

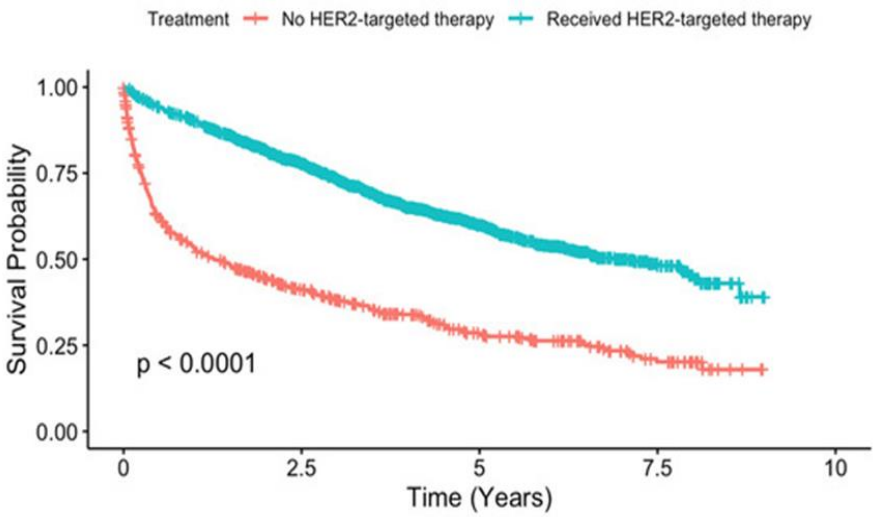

Figure 2. Estimated overall survival for patients with metastatic HR−/HER2+ breast cancer, stratified by receipt of HER2-directed treatment, displayed using Kaplan–Meier methodology.

Survival modeling demonstrated that exposure to HER2-targeted therapy was independently associated with substantially lower mortality after accounting for demographic, clinical, and institutional variables (HR = 0.52, 95% CI: 0.45–0.59; p < 0.001); **(Table 3).** This association remained robust across all adjusted analyses, indicating a strong survival advantage for patients receiving HER2-directed agents.

Age exerted a pronounced influence on survival, with progressively worse outcomes observed in older populations. Relative to patients aged 40–54 years, mortality risk increased among those aged 55–70 years (HR = 1.42, 95% CI: 1.21–1.67; p < 0.001) and was highest in individuals aged 71 years or older (HR = 1.62, 95% CI: 1.30–2.02; p < 0.001). Improvements in survival were also observed over time, as patients diagnosed in later calendar years demonstrated reduced mortality compared with earlier cohorts, including diagnoses made between 2014–2017 (HR = 0.75, p = 0.005) and 2018–2020 (HR = 0.84, p = 0.021).

Differences in survival outcomes were evident across racial categories. Black patients experienced a higher risk of death (HR = 1.22, p = 0.014), whereas patients grouped under other racial classifications showed a lower hazard of mortality (HR = 0.59, p = 0.012). Disease distribution at metastatic presentation further influenced prognosis. Metastatic involvement of the brain conferred the greatest adverse impact on survival (HR = 1.91, p < 0.001), followed by liver (HR = 1.49, p < 0.001) and bone metastases (HR = 1.18, p = 0.042).

Several therapeutic and care-delivery factors were associated with improved outcomes. Receipt of chemotherapy was strongly linked to prolonged survival (HR = 0.38, p < 0.001), as was surgical management of the primary tumor (HR = 0.57, p < 0.001). Insurance coverage influenced prognosis, with privately insured patients demonstrating superior survival compared with uninsured individuals (HR = 0.67, p = 0.005). Additionally, patients who received care across multiple Commission on Cancer–accredited facilities experienced a modest but statistically significant survival benefit (HR = 0.84, p = 0.048).

Table 3. Independent predictors of overall survival in metastatic HR−/HER2+ breast cancer identified through multivariable proportional hazards modeling.

Variable	Category	OR (95% CI)	p-Value
Age group	40–54	REF	—
	55–70	1.42 (1.21–1.67)	<0.001
	≥71	1.62 (1.30–2.02)	<0.001
Receipt of HER2-targeted therapy	No	REF	—
	Yes	0.52 (0.45–0.59)	<0.001
Race	White	REF	—
	Black	1.22 (1.04–1.43)	0.014
	South Asian	1.81 (0.74–4.42)	0.193
	Asian	1.31 (0.87–1.98)	0.201
	Other	0.59 (0.39–0.89)	0.012
Hispanic/Spanish origin	No	REF	—
	Yes	0.71 (0.43–1.02)	0.065
Year of diagnosis	2013–2015	REF	—
	2016–2018	0.75 (0.62–0.92)	0.005
	2019–2020	0.84 (0.72–0.96)	0.021
Urbanicity	Metropolitan	REF	—
	Urban	1.01 (0.85–1.22)	0.879
	Rural	1.03 (0.76–1.41)	0.841
Facility type	Community	REF	—
	Academic	0.84 (0.67–1.05)	0.132
	Comprehensive	0.98 (0.79–1.22)	0.874
	Network	0.97 (0.77–1.23)	0.816
Median household income	< USD 30,000	REF	—
	USD 30,000–34,999	1.14 (0.90–1.44)	0.257
	USD 35,000–45,999	1.09 (0.87–1.39)	0.429
	≥ USD 46,000	0.82 (0.66–1.02)	0.078
Insurance status	Not insured	REF	—
	Private insurance	0.67 (0.50–0.89)	0.005
	Medicare	0.90 (0.67–1.21)	0.483
	Medicaid	0.85 (0.62–1.16)	0.312

	Other government	0.63 (0.31–1.29)	0.215
Treatment at more than one CoC facility	No	REF	—
	Yes	0.84 (0.72–1.00)	0.048
Charlson Comorbidity Index score	0	REF	—
	1	1.05 (0.88–1.25)	0.604
	2	1.34 (0.98–1.82)	0.073
	≥3	1.37 (0.97–1.94)	0.072
Other treatments	Chemotherapy	0.38 (0.33–0.44)	<0.001
	Surgery at primary site	0.57 (0.47–0.67)	<0.001
Metastatic site	Bone	1.18 (1.00–1.39)	0.042
	Brain	1.91 (1.48–2.46)	<0.001
	Lung	1.07 (0.90–1.26)	0.452
	Liver	1.49 (1.27–1.76)	<0.001
	Other	1.50 (1.21–1.85)	<0.001

This analysis demonstrates a clear shift over time in the management of metastatic hormone receptor–negative, HER2-positive (HR−/HER2+) breast cancer, with a steady expansion in the use of HER2-targeted therapies between 2013 and 2020. This upward trend likely reflects both the introduction of more effective HER2-directed agents and increasing clinician familiarity with their benefits. International consensus statements, particularly those emerging from the ABC conferences since 2011, have played an important role in standardizing treatment approaches and reinforcing the use of HER2-targeted therapies in the metastatic setting [20]. However, despite overall growth in utilization, our findings reveal persistent inequities in treatment delivery that are closely tied to patient demographics and healthcare system characteristics.

Patient-related clinical factors were strongly associated with the receipt of HER2-targeted therapy. Individuals who were younger and had a lower comorbidity burden were more frequently treated with HER2-targeted agents, supporting previous observations that treatment intensity often declines with advancing age and increasing medical complexity [8, 9]. This pattern likely reflects clinician concerns regarding treatment tolerance, toxicity, and competing health risks, which may limit the use of aggressive therapies in older or more medically fragile patients [21, 22]. While such considerations are clinically relevant, they may also contribute to unintended undertreatment in certain populations.

Disparities by race and ethnicity were evident in our cohort. Compared with White patients, Black patients were less likely to receive HER2-targeted therapy, consistent with well-documented racial inequities in cancer treatment access and delivery [8, 10]. These differences raise concerns about systemic barriers that may disproportionately affect minority patients, including differences in referral patterns, healthcare access, implicit bias, and structural inequities within the healthcare system. Addressing these gaps remains critical to improving outcomes in historically underserved populations.

Economic factors also played a significant role in determining access to HER2-targeted therapies. Insurance coverage emerged as a key determinant, with privately insured patients having higher odds of receiving treatment than uninsured individuals, echoing prior research highlighting the importance of financial coverage in accessing modern oncologic therapies [23, 24]. Although trastuzumab is generally reimbursed by private insurers, Medicare, and Medicaid in the United States, substantial variability exists in coverage policies and patient cost-sharing requirements [25]. Administrative barriers such as prior authorization and step therapy may delay initiation, while Medicare beneficiaries often face high out-of-pocket expenses. Medicaid coverage differs by state, resulting in geographic variability, and uninsured patients frequently encounter prohibitive financial barriers despite the availability of assistance programs. Income level further influenced treatment access, with patients from higher-income households more likely to receive HER2-targeted therapy. Even with the availability of biosimilars, the financial burden associated with trastuzumab remains considerable, reinforcing the link between socioeconomic status and access to effective cancer treatments [26, 27].

Healthcare delivery factors also influenced treatment patterns. Patients treated at academic institutions and those residing in urban areas were more likely to receive HER2-targeted therapy, reflecting the centralization of specialized oncology care and advanced therapeutics within large medical centers [28-30]. In contrast, patients living in rural areas experienced lower treatment rates, likely due to limited access to subspecialty care, fewer oncology resources, and longer travel distances. These findings highlight the need for healthcare system–level interventions aimed at improving access to specialized cancer care outside of urban academic settings.

Survival analyses further underscored the clinical importance of HER2-targeted therapy. Patients who received these agents experienced significantly improved overall survival compared with those who did not, as demonstrated by Kaplan–Meier estimates. This survival advantage aligns with results from pivotal clinical trials, including the CLEOPATRA study, which established the efficacy of HER2-targeted therapy in combination with chemotherapy for metastatic HER2-positive breast cancer [5]. These findings reinforce the necessity of ensuring that eligible patients are not excluded from therapies that offer meaningful survival benefits.

Several limitations should be acknowledged. The NCDB records HER2 status as a binary variable and does not provide information on HER2 expression intensity (e.g., HER2+++), which may influence treatment selection and outcomes. As a result, we were unable to adjust for variation in HER2 expression that could affect clinical decision-making. In addition, the database does not capture treatment response, adverse events, or patient preferences, all of which may influence whether HER2-targeted therapy is initiated or continued. The NCDB is limited to Commission on Cancer–accredited facilities, potentially reducing the generalizability of these findings to non-accredited or resource-limited settings. Moreover, the database does not distinguish among specific HER2-targeted regimens, preventing evaluation of differences between single-agent and combination therapies. Finally, we were unable to determine the underlying reasons why approximately one-quarter of patients with metastatic HR−/HER2+ breast cancer did not receive HER2-targeted therapy despite its established benefit.

Conclusion

Overall, this study demonstrates that although the adoption of HER2-targeted therapies for metastatic HR−/HER2+ breast cancer has increased substantially over time, access to these treatments remains uneven. A combination of clinical characteristics, socioeconomic factors, and healthcare system variables continues to shape which patients ultimately receive HER2-targeted therapy. These disparities underscore the need for policy-driven and system-level solutions to reduce barriers to care, particularly among vulnerable and underserved populations [31]. Future research should focus on identifying modifiable contributors to treatment inequities and evaluating interventions such as expanded insurance coverage, improved access to oncology expertise in rural areas, and more inclusive treatment strategies for patients with greater comorbidity burdens. Addressing these challenges is essential to ensuring that advances in HER2-targeted therapy translate into improved outcomes for all patients, regardless of background or place of care.

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