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Disparities in HER2-Targeted Therapy Adoption and Survival Impact in Metastatic HR−/HER2+ Breast Cancer: NCDB Cohort Study

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ABSTRACT

Targeted inhibition of the HER2 pathway has dramatically enhanced survival rates among patients diagnosed with metastatic hormone receptor-negative, HER2-positive (HR−/HER2+) breast carcinoma. Nonetheless, the underlying influences guiding its clinical use are still not fully understood. This investigation explores clinical, demographic, and institutional predictors influencing the administration of HER2-focused treatments in individuals with metastatic HR−/HER2+ disease. Using the National Cancer Database (NCDB) covering years 2013-2020, a retrospective cohort design was employed. Participants were categorized according to whether they received HER2-directed therapy or not, with records lacking critical data removed. The study period was grouped into three segments—before 2015, 2016-2018, and 2019-2020—to mirror changes in therapeutic access across the U.S. Logistic regression (univariable and multivariable) identified determinants of treatment receipt, while survival was evaluated using Cox models and log-rank comparisons. Of 3060 individuals with metastatic HR−/HER2+ disease, 2318 (75.8%) underwent HER2-targeted therapy. Utilization climbed from 64.6% in 2013 to 80.9% by 2016, showing rapid early uptake, stayed elevated through 2018, and later stabilized near 75% between 2019 and 2020. Treatment receipt was more common among those diagnosed during 2016-2018 (OR 1.93, $p < 0.001$) and 2019-2020 (OR 1.88, $p < 0.001$), privately insured patients (OR 1.76, $p < 0.001$), and those managed at academic institutions (OR 1.39, $p = 0.031$). Lower odds were noted among patients aged ≥71 (OR 0.52, $p < 0.001$), Black patients (OR 0.78, $p = 0.018$), those covered by Medicare (OR 0.64, $p < 0.001$), and individuals treated in rural hospitals (OR 0.59, $p = 0.022$). Survival was significantly better for treated patients (median 5.08 vs. 1.27 years, log-rank $p < 0.001$), with reduced mortality risk (HR 0.52, $p < 0.001$). While uptake of HER2-targeted therapy has grown over time, measurable disparities in its distribution remain. Addressing socioeconomic and facility-related inequalities is crucial for equitable treatment access and improved outcomes across patient populations.

Keywords: HER2-directed therapy, Metastatic HR−/HER2+ breast carcinoma, Inequity in care, Survival outcomes

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Introduction

Metastatic hormone receptor-negative, HER2-positive (HR−/HER2+) breast carcinoma is an aggressive subtype within metastatic breast cancer (MBC) [1]. It exhibits rapid progression, limited sensitivity to standard chemotherapy, and generally poor outcomes, posing major therapeutic challenges [2-4]. The introduction of HER2-directed agents such as trastuzumab and pertuzumab has transformed care, yielding marked survival gains among patients with advanced disease [5-7]. Despite strong evidence of their efficacy, limited research has clarified what factors affect their utilization in metastatic HR−/HER2+ cases.

Recent analyses show that multiple dimensions—clinical, social, and institutional—shape access to systemic cancer treatments. For example, Pearson *et al*. reported that younger, white, and economically advantaged patients were more likely to obtain timely chemotherapy and related therapies [8]. Institutional setting also matters: individuals treated in academic, research, or private facilities tend to receive quicker interventions [8]. Morimoto

et al. linked reduced comorbidities, greater disease burden, and negative hormone receptor status with increased chemotherapy use [9]. Likewise, Caswell-Jin *et al*. observed that geography and community income influence treatment strategies, reflecting regional variations in resources and practice patterns [10].

Although much has been written about disparities in metastatic breast cancer treatment, few inquiries have focused on HER2-targeted therapy use specifically within metastatic HR−/HER2+ populations. The National Cancer Database (NCDB), which integrates detailed demographic and clinical data, provides a unique platform for assessing treatment patterns, particularly regarding HER2-based regimens [11-14]. Over the past decade, continual advancements in HER2 therapeutics have significantly changed management of metastatic HER2+ breast cancer [15-16]. New drugs, including tucatinib (approved 2019) and trastuzumab deruxtecan (approved 2020), expanded options for HR−/HER2+ patients late in the study timeline [17-19]. Their availability has notably influenced real-world prescribing trends [17-19]. Evaluating NCDB data from this era enables examination of evolving treatment dynamics, determinants of therapy selection, and their implications for survival.

The present study seeks to identify the clinical, demographic, and institutional variables that shape HER2-targeted therapy utilization in metastatic HR−/HER2+ breast cancer. Using national registry data, we aim to outline usage trends, uncover disparities in treatment access, and assess survival impact. Insights gained can inform future strategies to reduce inequities and enhance outcomes for patients facing this aggressive disease.

Materials and Methods

Study framework and dataset

This research drew upon the National Cancer Database (NCDB) to perform a retrospective cohort analysis of individuals diagnosed with metastatic HR−/HER2+ breast cancer from January 1, 2013, to December 31, 2020. Participants were classified into two categories: those who underwent HER2-directed therapy and those who did not receive such treatment. The grouping was determined using treatment codes and records included within the NCDB. Any case lacking essential clinical, socioeconomic, or institutional information was excluded.

During this time frame, trastuzumab and pertuzumab represented the primary frontline options for patients with metastatic HER2-positive disease [18]. The treatment spectrum later broadened with tucatinib, authorized in 2019, and trastuzumab deruxtecan, approved in 2020, thereby increasing therapeutic availability in the latter study years [18].

Patients presenting with HR+/HER2+ tumors were intentionally excluded to maintain a more uniform cohort, since their clinical management and biological response patterns differ from HR−/HER2+ disease.

Comparison of patient and institutional features

Demographic, clinical, and facility-based factors were examined between individuals receiving HER2-directed therapy and those not treated with such agents. The examined variables encompassed age, race, ethnicity, hospital category, population density (urban vs. rural), insurance type, local median income, ZIP code-level education, Charlson Comorbidity Index (CCI) score, metastatic sites, care at multiple institutions, use of other systemic therapies, and diagnosis year.

Analytical strategy

Associations with the use of HER2-targeted treatments were tested via univariate and multivariate logistic regression models. Predictors incorporated in the analysis included age group, racial/ethnic background, facility designation, geographic setting, payer status, neighborhood income and education level, CCI score, metastatic involvement, treatment at multiple centers, receipt of other therapies, and year of diagnosis.

Categorical variables were evaluated using the chi-square test, whereas t-tests were used for continuous data.

To explore survival outcomes, Kaplan-Meier plots were generated, and log-rank tests assessed differences in overall survival between treated and untreated groups. The Cox proportional hazards model was applied to determine the independent effect of HER2-targeted therapy on survival, adjusting for clinical, demographic, and institutional variables.

All analyses were conducted in RStudio (version 2023.12.0 + 369), adopting a significance level of $p < 0.05$.

Results and Discussion

Evolution of HER2-directed therapy use in metastatic HR−/HER2+ breast cancer

The frequency of HER2-targeted therapy administration in metastatic HR−/HER2+ breast cancer rose markedly from 64.6% in 2013 to 80.9% in 2016 ($p < 0.001$) **(Figure 1)**. A modest decline was noted in 2017 (79.7%), yet the rate stayed high through 2020, leveling off at approximately 75.1%. This trajectory indicates a steady adoption of HER2-targeted treatments across the observed period.

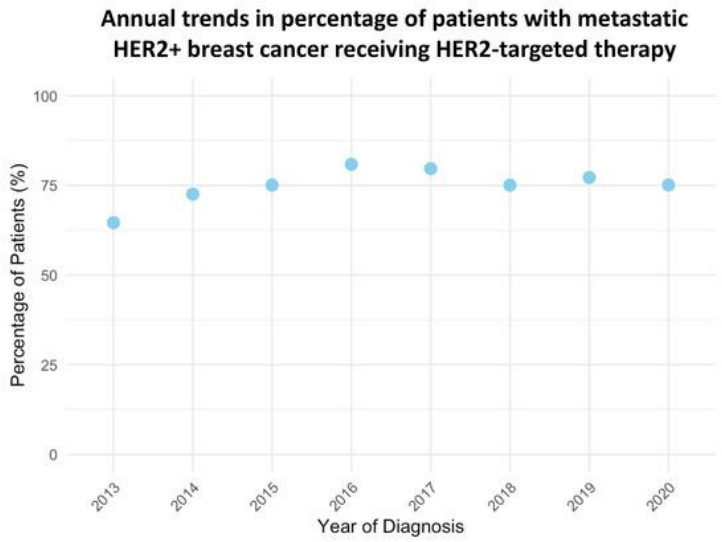

Figure 1. Yearly proportion of metastatic HR−/HER2+ breast cancer patients receiving HER2-directed therapy from 2013-2020 ($p < 0.001$, linear model).

Clinical and institutional profile of the study cohort

From 2013-2020, the NCDB identified 3060 patients with metastatic HER2-positive breast cancer, of whom 2318 (75.8%) received HER2-targeted agents and 742 (24.2%) did not **(Table 1)**.

Table 1. Patient demographics, disease features, socioeconomic indicators, and hospital characteristics associated with HER2-targeted therapy use.

Characteristic	No HER2-Directed Therapy (N = 742)	Received HER2-Directed Therapy (N = 2318)	p-Value
Age group			<0.001
40-54	146 (19.6%)	789 (34.0%)	
55-70	332 (44.5%)	1132 (48.8%)	
71+	268 (35.9%)	397 (17.1%)	
Year of Diagnosis			<0.001
2013-2015	247 (33.1%)	608 (26.2%)	
2016-2018	264 (35.4%)	960 (41.4%)	
2019-2020	235 (31.5%)	750 (32.3%)	
Race (%)			0.041
White	545 (73.1%)	1784 (77.0%)	
Black	151 (20.2%)	385 (16.6%)	
Asian	12 (1.6%)	42 (1.8%)	
South Asian	25 (3.4%)	82 (3.5%)	
Other	4 (0.5%)	14 (0.6%)	
Unknown	9 (1.2%)	11 (0.5%)	
Hispanic/Spanish Origin (%)			0.004
Yes	46 (6.2%)	148 (6.4%)	
No	677 (90.8%)	2140 (92.3%)	
Unknown	23 (3.1%)	30 (1.3%)	
Facility Type (%)			<0.001
Community	90 (12.1%)	167 (7.2%)	

Comprehensive	301 (40.3%)	835 (36.0%)	
Academic	196 (26.3%)	840 (36.2%)	
Network	159 (21.3%)	476 (20.5%)	
Urbanicity (%)			0.541
Metropolitan	614 (82.3%)	1909 (82.4%)	
Rural	27 (3.6%)	103 (4.4%)	
Urban	105 (14.1%)	306 (13.2%)	
Insurance Status (%)			<0.001
Not Insured	37 (5.0%)	100 (4.3%)	
Private Insurance	211 (28.3%)	1130 (48.7%)	
Medicaid	91 (12.2%)	325 (14.0%)	
Medicare	384 (51.5%)	719 (31.0%)	
Other Government	7 (0.9%)	27 (1.2%)	
Unknown	16 (2.1%)	17 (0.7%)	
Treatment at >1 CoC facility (%)			<0.001
Yes	91 (12.2%)	477 (20.6%)	
No	655 (87.8%)	1841 (79.4%)	
Median Income (%)			<0.001
<USD 30, 000	135 (18.1%)	226 (9.7%)	
USD 30, 000-USD 34, 999	99 (13.3%)	306 (13.2%)	
USD 35, 000-USD 45, 999	143 (19.2%)	529 (22.8%)	
≥USD 46, 000	252 (33.8%)	887 (38.3%)	
Unknown	117 (15.7%)	370 (15.9%)	
Charlson Comorbidity Index Score (%)			<0.001
0	559 (74.9%)	1954 (84.3%)	
1	112 (15.0%)	264 (11.4%)	
2	36 (4.8%)	65 (2.8%)	
≥3	39 (5.2%)	35 (1.5%)	
Metastatic Site (%)			
Bone	301 (40.3%)	998 (43.0%)	0.208
Brain	71 (9.5%)	118 (5.1%)	<0.001
Liver	188 (25.2%)	652 (28.1%)	0.130
Lung	190 (25.4%)	526 (22.7%)	0.131
Other	100 (13.4%)	190 (8.2%)	<0.001
Other Treatments (%)			
Chemotherapy	282 (37.8%)	2008 (86.6%)	<0.001
Surgery at primary site	98 (13.1%)	589 (25.4%)	<0.001

Individuals administered HER2-targeted therapy were generally younger, with larger proportions aged 40-54 years (34.0% vs. 19.6%, $p < 0.001$) and 55-70 years (48.8% vs. 44.5%, $p < 0.001$), and fewer aged 71 years or older (17.1% vs. 35.9%, $p < 0.001$). Treatment was more prevalent among patients diagnosed in 2016-2018 (41.4%) and 2019-2020 (32.3%), compared to 2013-2015 (26.2%, $p < 0.001$).

Differences by race were evident: a greater proportion of recipients were White (77.0% vs. 73.1%, $p = 0.041$) and fewer were Black (16.6% vs. 20.2%, $p = 0.041$). Slightly higher rates of Hispanic ethnicity were observed in the treated group (6.4% vs. 6.2%, $p = 0.004$).

Insurance coverage patterns varied substantially. Patients on HER2-targeted therapy were more frequently insured through private providers (48.7% vs. 28.3%, $p < 0.001$) or Medicaid (14.0% vs. 12.2%, $p < 0.001$), while non-recipients were more likely to depend on Medicare (51.5% vs. 31.0%, $p < 0.001$) or to be uninsured (5.0% vs. 4.3%, $p < 0.001$).

Economically, HER2-treated individuals tended to reside in areas with higher median income, with more earning ≥ USD 46, 000 (38.3% vs. 33.8%, $p < 0.001$) and fewer earning < USD 30, 000 (9.7% vs. 18.1%, $p < 0.001$).

With respect to treatment facilities, HER2 therapy was more commonly delivered in academic centers (36.2% vs. 26.3%, $p < 0.001$) and comprehensive cancer hospitals (36.0% vs. 40.3%, $p < 0.001$), and less often in community-

based institutions (7.2% vs. 12.1%, $p < 0.001$). A greater fraction of HER2-treated patients were managed across multiple CoC-accredited facilities (20.6% vs. 12.2%, $p < 0.001$).

Clinically, those who received HER2 therapy had fewer comorbidities, with CCI = 0 observed in 84.3% compared to 74.9% of non-treated individuals ($p < 0.001$), and CCI ≥ 3 in 1.5% vs. 5.2%, respectively ($p < 0.001$). Patterns of metastasis also differed: brain metastases were less common in treated patients (5.1% vs. 9.5%, $p < 0.001$), whereas differences in bone, liver, and lung involvement were not statistically significant.

HER2-targeted therapy recipients were far more likely to undergo chemotherapy (86.6% vs. 37.8%, $p < 0.001$) and surgical removal of the primary tumor (25.4% vs. 13.1%, $p < 0.001$).

Determinants of HER2-targeted therapy administration in metastatic HR−/HER2+ breast cancer

The multivariable logistic regression model revealed several parameters that influenced whether patients with HER2-positive metastatic breast cancer received HER2-targeted therapy **(Table 2)**.

Age was one of the strongest determinants. Individuals aged 71 years or older were far less likely to be prescribed HER2-targeted drugs compared with the 40-54-year reference group (OR = 0.41, 95% CI: 0.30-0.57, $p < 0.001$). Those aged 55-70 years also demonstrated reduced odds, though to a lesser extent (OR = 0.76, 95% CI: 0.60-0.96, $p = 0.025$).

Year of diagnosis significantly influenced treatment trends. Compared to patients diagnosed between 2013 and 2015, those identified in 2016-2018 (OR = 1.93, 95% CI: 1.40-2.65, $p < 0.001$) and 2019-2020 (OR = 1.88, 95% CI: 1.35-2.62, $p < 0.001$) were more likely to receive HER2-directed therapy, reflecting expanded clinical use over time.

Table 2. Multivariate logistic regression examining variables influencing HER2-targeted therapy in metastatic HER2-positive cases.

	OR (95% CI)	***p*-Value**
Age group		
40-54	REF	
55-70	0.76 (0.60-0.96)	0.025
71+	0.41 (0.30-0.57)	<0.001
Year of Diagnosis		
2013-2015	REF	
2016-2018	1.93 (1.40-2.65)	<0.001
2019-2020	1.88 (1.35-2.62)	<0.001
Race		
White	REF	
Black	0.81 (0.67-0.95)	0.043
Asian	0.92 (0.44-1.94)	0.831
South Asian	0.85 (0.22-3.27)	0.817
Other	0.91 (0.53-1.59)	0.751
Hispanic/Spanish Origin		
No	REF	
yes	0.77 (0.51-1.17)	0.222
Facility Type		
Community	REF	
Comprehensive	1.47 (1.03-2.10)	0.035
Academic	2.57 (1.77-3.73)	<0.001
Network	1.73 (1.17-2.56)	0.005
Urbanicity (%)		
Metropolitan	REF	
Rural	1.30 (0.77-2.19)	0.326
Urban	1.13 (0.83-1.53)	0.455
Insurance Status (%)		
Not Insured	REF	
Private Insurance	1.79 (1.17-2.73)	0.007
Medicaid	1.26 (0.74-2.15)	0.393
Medicare	0.96 (0.57-1.62)	0.884

Other Government	1.09 (0.36-3.35)	0.875
Median Income (%)		
<USD 30, 000	REF	
USD 30, 000-USD 34, 999	1.75 (1.19-2.56)	0.004
USD 35, 000-USD 45, 999	1.65 (1.11-2.47)	0.004
≥USD 46000	1.78 (1.24-2.76)	0.010
Charlson Comorbidity Index Score (%)		
0	REF	
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
Treatment at >1 CoC facility (%)		
No	REF	
Yes	1.46 (1.10-1.94)	0.008
Metastatic Site (%)		
Bone	0.99 (0.78-1.28)	0.976
Brain	0.43 (0.29-0.64)	<0.001
Liver	0.98 (0.76-1.26)	0.876
Lung	1.00 (0.77-1.29)	0.992
Other	0.46 (0.27-0.89)	0.008
Other Treatments (%)		
Chemotherapy	9.53 (7.65-11.86)	<0.001
Surgery at primary site	1.28 (0.97-1.68)	0.083

When examining socioeconomic determinants, racial inequities were present. Black patients were less frequently administered HER2 therapy than White patients (OR = 0.81, 95% CI: 0.67-0.95, p = 0.043).

Insurance coverage was another strong predictor — those holding private insurance were considerably more likely to receive HER2 therapy than uninsured individuals (OR = 1.79, 95% CI: 1.17-2.73, p = 0.007).

Income also demonstrated a clear gradient effect. Participants earning USD 30, 000-34, 999 (OR = 1.75, 95% CI: 1.19-2.56, p = 0.004), USD 35, 000-45, 999 (OR = 1.65, 95% CI: 1.11-2.47, p = 0.004), and ≥USD 46, 000 (OR = 1.78, 95% CI: 1.24-2.76, p = 0.010) were progressively more likely to undergo targeted treatment than those earning below USD 30, 000.

In terms of facility type, patients managed in academic hospitals had a markedly higher probability of receiving HER2 therapy relative to those treated at community institutions (OR = 2.57, 95% CI: 1.77-3.73, p < 0.001). Individuals treated at comprehensive centers (OR = 1.47, 95% CI: 1.03-2.10, p = 0.035) or network sites (OR = 1.73, 95% CI: 1.17-2.56, p = 0.005) also displayed elevated odds compared to the same baseline.

Among clinical parameters, metastatic involvement played an important role. The presence of brain metastasis was associated with a much lower probability of HER2 therapy (OR = 0.43, 95% CI: 0.29-0.64, p < 0.001). Conversely, those who underwent chemotherapy were almost ten times more likely to receive HER2-targeted agents (OR = 9.53, 95% CI: 7.65-11.86, p < 0.001).

Primary-site surgery was not significantly correlated (OR = 1.28, 95% CI: 0.97-1.68, p = 0.083).

Patients with Charlson Comorbidity Index scores ≥3 were less often treated with HER2 therapy compared with those having a score of 0 (OR = 0.40, 95% CI: 0.22-0.73, p = 0.002).

Survival outcomes associated with HER2-targeted therapy

Survival analysis demonstrated a clear advantage among patients receiving HER2-directed therapy. Kaplan-Meier estimates revealed significantly longer survival for those treated compared to untreated counterparts **(Figure 2)**, (p < 0.001).

The median overall survival was 1.27 years (95% CI: 0.97-1.82) for patients not receiving therapy, while those treated with HER2-targeted drugs achieved a median survival of 5.08 years (95% CI: 4.25-6.03).

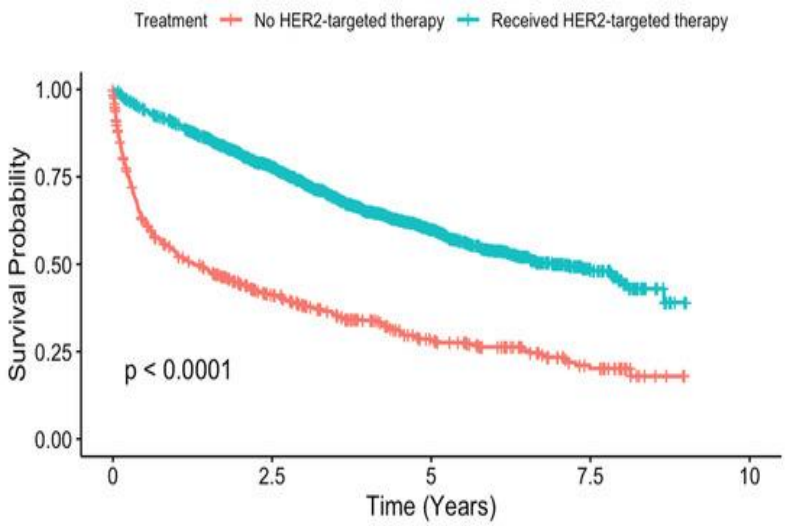

Figure 2. Kaplan-Meier survival comparison of metastatic HR−/HER2+ breast cancer patients receiving versus not receiving HER2-targeted therapy.

A Cox proportional hazards model, adjusted for demographic, clinical, and institutional variables, confirmed that HER2 therapy was independently associated with better survival (HR: 0.52, 95% CI: 0.45-0.59, p < 0.001) **(Table 3)**.

Further influencing survival were age and year of diagnosis. Mortality risk was elevated for patients aged 55-70 years (HR: 1.42, 95% CI: 1.21-1.67, p < 0.001) and ≥71 years (HR: 1.62, 95% CI: 1.30-2.02, p < 0.001) compared with those aged 40-54. Improved survival was noted in individuals diagnosed during 2014-2017 (HR: 0.75, 95% CI: 0.62-0.92, p = 0.005) and 2018-2020 (HR: 0.84, 95% CI: 0.72-0.96, p = 0.021).

Race was also a relevant factor: Black patients faced higher mortality (HR: 1.22, 95% CI: 1.04-1.43, p = 0.014), whereas patients of other racial groups had a survival benefit (HR: 0.59, 95% CI: 0.39-0.89, p = 0.012).

Bone (HR: 1.18, 95% CI: 1.00-1.39, p = 0.042), brain (HR: 1.91, 95% CI: 1.48-2.46, p < 0.001), and liver metastases (HR: 1.49, 95% CI: 1.27-1.76, p < 0.001) were associated with poorer survival outcomes.

Conversely, both chemotherapy (HR: 0.38, 95% CI: 0.33-0.44, p < 0.001) and primary-tumor surgery (HR: 0.57, 95% CI: 0.47-0.67, p < 0.001) contributed to improved overall survival.

In addition, insurance type affected longevity — patients with private coverage showed better survival outcomes (HR: 0.67, 95% CI: 0.50-0.89, p = 0.005). Treatment at more than one CoC-accredited facility was also linked to slightly improved outcomes (HR: 0.84, 95% CI: 0.72-1.00, p = 0.048).

Table 3. Cox regression results for predictors of overall survival in patients with metastatic HR−/HER2+ breast cancer.

Characteristic	OR (95% CI)	p-Value
Received HER2-targeted therapy		
No	REF	
Yes	0.52 (0.45-0.59)	<0.001
Age group		
40-54	REF	
55-70	1.42 (1.21-1.67)	<0.001
71+	1.62 (1.30-2.02)	<0.001
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
Race		
White	REF	
Black	1.22 (1.04-1.43)	0.014
Asian	1.31 (0.87-1.98)	0.201
South Asian	1.81 (0.74-4.42)	0.193

Other	0.59 (0.39-0.89)	0.012
Hispanic/Spanish Origin		
No	REF	
Yes	0.71 (0.43-1.02)	0.065
Facility Type		
Community	REF	
Comprehensive	0.98 (0.79-1.22)	0.874
Academic	0.84 (0.67-1.05)	0.132
Network	0.97 (0.77-1.23)	0.816
Urbanicity		
Metropolitan	REF	
Rural	1.03 (0.76-1.41)	0.841
Urban	1.01 (0.85-1.22)	0.879
Insurance Status		
Not Insured	REF	
Private Insurance	0.67 (0.50-0.89)	0.005
Medicaid	0.85 (0.62-1.16)	0.312
Medicare	0.90 (0.67-1.21)	0.483
Other Government	0.63 (0.31-1.29)	0.215
Median Income		
<USD 30, 000	REF	
USD 30, 000-USD 34, 999	1.14 (0.90-1.44)	0.257
USD 35, 000-USD 45, 999	1.09 (0.87-1.39)	0.429
≥USD 46, 000	0.82 (0.66-1.02)	0.078
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
Treatment at >1 CoC facility		
No	REF	
Yes	0.84 (0.72-1.00)	0.048
Metastatic Site		
Bone	1.18 (1.00-1.39)	0.042
Brain	1.91 (1.48-2.46)	<0.001
Liver	1.49 (1.27-1.76)	<0.001
Lung	1.07 (0.90-1.26)	0.452
Other	1.50 (1.21-1.85)	<0.001
Other Treatments		
Chemotherapy	0.38 (0.33-0.44)	<0.001
Surgery at primary site	0.57 (0.47-0.67)	<0.001

The outcomes of this research illustrate the shifting trends in the application of HER2-directed treatments among patients diagnosed with metastatic hormone receptor-negative, HER2-positive (HR−/HER2+) breast cancer. Between 2013 and 2020, there was a substantial rise in the administration of HER2-targeted drugs, corresponding with improvements in therapeutic innovation and evolving clinical standards. Guidance issued through the ABC conferences since 2011 has notably influenced worldwide protocols and clinical recommendations, likely contributing to the expanding implementation of HER2-targeted regimens [20]. Despite their increasing use, inequities remain evident, as patient access continues to differ considerably based on sociodemographic and institutional characteristics. These observations reveal ongoing challenges in equitable oncology care and emphasize the necessity of initiatives promoting fair and inclusive distribution of advanced cancer therapies.

Consistent with prior research, our findings reaffirm that age, comorbidities, and disease extent strongly determine the probability of receiving HER2-based therapy [8, 9]. Younger individuals and those with fewer accompanying health conditions were substantially more likely to be treated with HER2-directed agents, aligning with general clinical patterns where younger, healthier populations are more frequently selected for intensive treatment

modalities [21, 22]. This likely reflects both physician judgment and the assessment of patient tolerance for complex therapeutic regimens, a major consideration in managing metastatic breast cancer.

Racial and ethnic inequalities in therapy access were also apparent. White patients demonstrated a higher likelihood of receiving HER2-targeted drugs than Black patients, echoing the wider disparities in cancer management that are extensively documented in the literature [8, 10]. These results are particularly troubling, as they suggest that systemic healthcare imbalances and differences in provider-patient dynamics may restrict minority groups' opportunities to benefit from advanced therapeutic interventions.

Socioeconomic variables, including insurance coverage and income level, emerged as significant indicators of HER2 therapy utilization. Individuals with private insurance showed a greater probability of receiving these treatments compared to uninsured patients, supporting prior evidence that insurance access is a critical factor influencing availability of specialized oncology care [23, 24]. In the U.S., trastuzumab is commonly reimbursed through private insurers, Medicare, and Medicaid, though the extent of coverage varies by provider, policy, and geographic region [25]. Private insurers may enforce preauthorization or step-therapy protocols, delaying initiation, while Medicare beneficiaries often encounter notable out-of-pocket expenses such as coinsurance and deductibles. Medicaid benefits differ by state, producing substantial regional inconsistencies in access. Additionally, a notable proportion of individuals remain without insurance, encountering significant financial hurdles to obtaining trastuzumab. Although patient assistance programs can offset some expenses, their availability is inconsistent, leaving many patients unable to afford treatment. Likewise, individuals from higher-income groups had enhanced access to HER2-targeted drugs, suggesting that economic resources still heavily influence therapeutic accessibility. Despite the introduction of biosimilar formulations, trastuzumab remains financially burdensome, and treatment availability continues to hinge on both socioeconomic status and insurance security [26, 27]. These findings highlight the pressing need to confront financial and insurance-based barriers to ensure equitable access to modern cancer therapies across all populations.

Geographic setting also played an essential role in treatment allocation. Patients managed in academic or urban medical centers were more frequently administered HER2-targeted drugs, illustrating the concentration of specialized oncology resources in these facilities [28-30]. This trend supports the perspective that institutional infrastructure significantly determines treatment accessibility. In contrast, individuals residing in rural areas, where specialized oncology services are limited, were less likely to receive HER2-targeted therapy. This disparity underscores the need for focused policy measures and healthcare delivery strategies aimed at expanding access to advanced treatment modalities within rural and medically underserved communities.

The survival results associated with HER2-directed treatments in this research were highly favorable. Kaplan-Meier survival curves revealed that individuals receiving HER2-targeted therapy achieved markedly longer survival durations compared with those who did not undergo such treatment. This finding corresponds closely with outcomes from major clinical investigations—most notably, the CLEOPATRA trial—which demonstrated the survival advantage of integrating HER2-directed drugs with chemotherapy in metastatic HER2-positive breast cancer [5]. These improvements in overall survival highlight the critical need to ensure equal and widespread access to HER2-based treatment regimens, given their substantial potential to enhance prognosis in this aggressive disease subtype.

Despite these compelling findings, the study has several noteworthy limitations. A major constraint is that the NCDB identifies whether tumors are HER2-positive or HER2-negative but lacks detailed information on the extent of HER2 expression (e.g., HER2+++). Since the degree of HER2 amplification is an important criterion influencing clinical recommendations and therapeutic decision-making, the absence of this detailed data may have influenced our survival estimates. Consequently, our analysis could not fully adjust for the effect of HER2 expression intensity on treatment allocation or outcomes in the regression models. Furthermore, although the NCDB encompasses a large spectrum of clinical and demographic variables, it omits other relevant aspects—such as individual treatment response, patient preferences, and physician discretion—that may shape therapeutic choices. Another limitation relates to the NCDB's emphasis on Commission on Cancer (CoC)-accredited hospitals, which may restrict the applicability of our results to non-academic or rural medical settings, where treatment delivery patterns can differ considerably.

Moreover, the database does not differentiate between specific HER2-targeted drugs or treatment combinations—for instance, trastuzumab alone versus trastuzumab administered with pertuzumab—thereby limiting our ability to evaluate regimen-specific survival outcomes. An additional challenge is the lack of insight into why approximately 25% of patients with metastatic HR−/HER2+ breast cancer did not receive HER2-targeted therapy,

despite its well-documented impact on survival. This gap underscores the need for further investigation into treatment decision barriers within this patient population.

Conclusion

In summary, the use of HER2-targeted agents in metastatic HR−/HER2+ breast cancer has expanded significantly over the past decade; however, our analysis reveals persistent inequities in treatment accessibility. Clinical, socioeconomic, and institutional variables all substantially influence which patients ultimately receive HER2-targeted therapy. These disparities emphasize the necessity for policy-driven interventions and equity-focused strategies aimed at minimizing treatment barriers, particularly for marginalized and underrepresented groups [31]. Future studies should concentrate on uncovering the underlying drivers of these disparities and on devising effective approaches to enhance access—such as broadening insurance coverage, improving healthcare infrastructure in rural communities, and ensuring that patients with multiple comorbidities are not systematically excluded from potentially life-prolonging treatments. Addressing these systemic gaps will be vital to ensuring that the therapeutic benefits of HER2-targeted treatments are equitably distributed, thereby improving overall survival outcomes and fostering greater health equity in the management of metastatic HR−/HER2+ breast cancer.

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