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ORIGINAL RESEARCH

Impact of Delaying Disease Recurrence on Economic Burden in Patients with HER2+ Early-Stage Breast Cancer (eBC)

Nicole Princic[1], Eleanor Faherty[2], Meghan Moynihan[1], Caroline Henriques[2], Sandhya Mehta[1]

[1]Data Research & Analytics, Real World Data, MarketScan by Merative, Ann Arbor, MI, USA; [2]HEOR & RWE, US Medical Affairs, Daiichi Sankyo, Inc., Basking Ridge, NJ, USA

Correspondence: Sandhya Mehta, Daiichi Sankyo, Inc., 211 Mt. Airy Road, Basking Ridge, NJ, 07920, USA, Tel +1 908 992 6400, Email sandhya.mehta@daiichisankyo.com

Purpose: This study aimed to assess neoadjuvant (neo), post-neo, and adjuvant (adj) treatment (tx) patterns, recurrence rates, and the impact of recurrence timing on the cumulative cost burden among HER2+ early breast cancer (eBC) patients.

Methods: Merative™ MarketScan® Databases were used to identify adults newly diagnosed with eBC between 1/1/2017-9/30/2022 with ≥1 HER2 targeted treatment following BC date. Surgery within a year of the BC date delineated neo and post-neo/adj periods before and after the surgery date. Recurrence was reported during the post-surgery period and was defined as evidence of additional chemotherapy treatment, metastasis, or end-of-life care. Generalized linear model (GLM) (gamma distribution and log link) was used to assess the impact of disease recurrence on cumulative 3-year total all-cause costs during the post-surgery period.

Results: A total of 3745 patients with HER2+ eBC were included in the study (mean age 53.7 yrs): 57.4% (n=2151) with adj tx only, 40.2% (n=1504) with neo and post-neo tx, 1.9% (n=70) with surgery only, and 0.5% (n=20) neo tx only. During follow-up (median duration post-surgery: 2 years), the rate of first recurrence was highest for surgery only (70.0%) and similar for adj only (16.0%) and neo and post-neo tx (14.3%) cohorts. GLM showed that the cumulative cost burden following surgery was higher among patients who experienced the first recurrence in <12 months vs no recurrence ($348,834 vs $265,279). Patients with chemo only as adj tx had a higher cumulative cost burden (Risk Ratio [RR] 1.28; p <0.001) than those with HER2 targeted treatment; and patients with neo tx had a lower cost burden (RR 0.85, p <0.001) compared with those with no neo tx.

Conclusion: Delays in recurrence were associated with lower cumulative cost burden. Study findings highlight that the appropriate use of more effective HER2 targeted treatments that delay the time of first recurrence in neoadjuvant and adjuvant settings may improve patient outcomes and reduce the long-term healthcare burden associated with BC.

Keywords: breast cancer, neoadjuvant therapy, adjuvant drug therapy, recurrence, health care costs

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer among women in the United States, accounting for nearly 30% of all new female cancers each year. In 2025, the American Cancer Society estimates about 316,950 new cases of invasive BC and 42,170 attributable deaths.[1] BC is a heterogeneous disease classified by molecular subtype based on genetic expression. The subtype with increased expression of the human epidermal growth factor receptor on the surface of cancer cells (HER2+) constitutes between 15–20% of early stage BC (eBC).[2]

HER2+ breast cancers are historically associated with poorer patient outcomes, including shorter disease-free and overall survival.[3,4] Treatment with trastuzumab and other HER2-targeted therapies has led to major survival gains for patients with HER2+ eBC.[5–7] Trastuzumab added to chemotherapy in early stage HER2+ breast cancer reduced recurrence and mortality by a third.[8] Specifically, neoadjuvant treatment consisting of HER2-targeted therapy has become the standard of care for HER2+ eBC to downsize the tumor before surgery for high-risk patients, characterized by tumors larger than 2 cm or with axillary lymph node involvement.[4,9,10] Neoadjuvant treatment also provides an opportunity to

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assess the response to therapy and thus guide the choice of post-operative therapy, referred to as post-neoadjuvant or adjuvant depending on whether neoadjuvant therapy was present, respectively.

Real-world studies exploring the treatment patterns and health care burden of treatment for patients with HER2+ eBC are limited. The most relevant publication, using administrative claims data from 2008–2013 among less than a thousand patients, reported nearly one-third of patients did not receive HER2-targeted therapy even when considered standard of care.[11] More recent reports among patients with high-risk eBC showed nearly 40% without neoadjuvant treatment.[12] With the advent of new HER2+ targeted treatment as a potential option for treating HER2+ eBC,[13,14] robust contemporary real-world analyses are needed to understand current treatment practices and unmet needs as it relates to the risk of recurrence.[4]

There remains a significant risk of recurrence: depending on the initial stage, tumor biology, and initial treatment received, up to 25% of patients with HER2+ eBC treated with HER2-directed therapy experience the first recurrence within 10 years.[5] Breast cancer recurrence within 5 years varies from 6–25% depending on many factors, including age, cancer stage, cancer type, and treatment.[15] Studies have also highlighted the increased clinical and economic burden of disease progression.[16,17] A study using claims data from 2006–2014 reported per-patient-per-month costs twice as high for progressors versus non progressors and longer time to progression was associated with lower healthcare costs.[16] However, these studies are among patients with metastatic breast cancer and not eBC. There is a gap in understanding the impact of disease recurrence and its timing on cumulative cost burden of HER2+ eBC.

The current study used recent real-world data reflecting current management of HER2+ eBC disease to understand patterns of care and associated resource burden. Specifically, this study aimed to assess neoadjuvant, post-neoadjuvant, and adjuvant treatment patterns, the rate of first recurrence, and the impact of recurrence timing on the cumulative cost burden among patients with HER2+ eBC.

Methods

Study Design and Data Source

This retrospective cohort study utilized data from the Merative™ MarketScan® Commercial and Medicare Databases between July 1, 2016 and September 30, 2023 (study period). The Commercial and Medicare databases are geographically dispersed, including individuals from all four United States Census Regions (Northeast, Midwest, South, and West), and thus, provide a nationally representative data sample of Americans. The Medicare database includes patients who are Medicare-eligible retirees with employer-sponsored Medicare Supplemental and Medicare Advantage Plans. Both databases provide detailed healthcare resource utilization (HCRU), outcomes, and cost data for medical services performed in both the inpatient and outpatient settings. Medical claims are linked to outpatient prescription drug claims and person-level enrollment data via unique enrollee identifiers. All variables were defined using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes, Current Procedural Terminology (CPT) 4th edition codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDC).

Patient Selection and Cohort Assignment

Adult patients with at least two medical claims at least 30 days apart with a diagnosis code for BC (ICD-10-CM C50* Malignant neoplasm of the breast) between 1/1/2017-9/30/2022 (earliest diagnosis claim = BC date) and ≥1 HER2 targeted treatment on or following the BC date were selected for inclusion in the study. See Supplemental Table 1 for HER2 targeted treatments. Surgery (ie, mastectomy or lumpectomy) within a year of the BC date delineated neoadjuvant from the post-neoadjuvant and adjuvant periods, before and after surgery date respectively, in which treatment patterns were described (earliest surgery claim = surgery date). Additionally, patients were required to have continuous enrollment with medical and pharmacy benefits in the six months before the BC date (pre-diagnosis period), from the BC date through the surgery date (pre-surgery period), and at least six months after the surgery date (unless evidence of hospital discharge status of death), and were followed for a variable length (minimum six months unless inpatient death) after the date of surgery until the earliest of end of enrollment, study end, or inpatient death (post-surgery period). Patients were

excluded if they had any medical claims for BC or secondary malignancy prior to the BC date, primary cancer other than BC prior to the surgery date, or secondary malignancy from the BC date through 30 days after the surgery date.

The overall HER2+ eBC population was subdivided into cohorts of patients with and without neoadjuvant and post-neoadjuvant/adjuvant treatments, identified during the pre- and post-surgery periods, respectively (neoadjuvant only, neoadjuvant and post-neoadjuvant, adjuvant only, and surgery only). Treatments as evidenced by claims for the prescription (NDC code) or administration (HCPCS code) included approved systemic therapies for the treatment of breast cancer.[9,18,19] See Supplemental Table 2 for the included systemic therapies.

Neoadjuvant therapy was identified during the pre-surgery period, extending from the date of BC to the day before the surgery date. Post-neoadjuvant and adjuvant therapies were identified during the post-surgery period inclusive of the date of surgery and with a start date up to 120 days after surgery. This period is a generous interpretation of clinical recommendations to initiate adjuvant therapy within 8 weeks following surgery.[20] If no post-neoadjuvant or adjuvant therapy was identified during this period, patients were classified as such.

Outcomes

Baseline patient demographics on the surgery date and clinical characteristics during the 6-month pre-diagnosis period were reported for each treatment cohort. Treatment utilization was captured during the neoadjuvant, post-neoadjuvant and adjuvant periods.

The rate of first recurrence was reported for each treatment cohort during the post-surgery period as defined by evidence of additional chemotherapy treatment (after 90-day gap following discontinuation of all post-neoadjuvant /adjuvant therapy accounting for +30 days of clinical benefit of last therapy or outside of the 120-day post-neoadjuvant /adjuvant window), metastasis (medical claim with diagnosis code for secondary malignancy), or end-of-life care (claim indicating hospice care).

All-cause and BC-specific HCRU and associated costs were reported during the variable-length post-surgery period, stratified by evidence of recurrence. BC-specific HCRU and costs were determined based on 1) inpatient admissions with a primary diagnosis of BC, 2) outpatient claims with a diagnosis of BC in any position, 3) inpatient or outpatient claims with procedure codes for radiation, immunohistochemistry, mastectomy, lumpectomy surgery, or office-administered BC treatments, and 4) BC-specific pharmacy claims. All dollar estimates were inflated to 2022 dollars using the Medical Care Component of the Consumer Price Index.

Analysis

The analyses were presented by treatment cohort, with the primary treatment cohorts being the neoadjuvant and post-neoadjuvant cohorts and the adjuvant-only cohort. Categorical variables were presented as the count and percentage of patients in each category; continuous variables were summarized as means and standard deviation (SD). Kaplan-Meier analysis was used to measure the time from surgery to recurrence. Generalized linear models (GLM) (gamma distribution and log link) adjusting for patient demographics and treatment type were utilized to assess the impact of the first disease recurrence (<12 or 12–36 months from the surgery date) on cumulative 3-year total all-cause costs during the post-surgery period.

Results

Patient Characteristics

A total of 3745 patients with HER2+ eBC were included in this study (Figure 1). Of these, 57.4% (n=2151) had adjuvant treatment only, 40.2% (n=1504) had neoadjuvant and post-neoadjuvant treatments, 1.9% (n=70) had surgery only, and 0.5% (n=20) had neoadjuvant treatment only (Figure 2).

Mean age was slightly younger for patients receiving neoadjuvant and post-neoadjuvant treatment (51.3 years) compared to adjuvant treatment only (55.2 years) and surgery only (56.5 years) (Table 1). Majority of patients (>50%) had a Comprehensive/EPO/PPO insurance plan type. About a quarter of patients had hypertension; most clinical conditions increased in prevalence from neoadjuvant and post-neoadjuvant to adjuvant only to surgery-only cohorts,

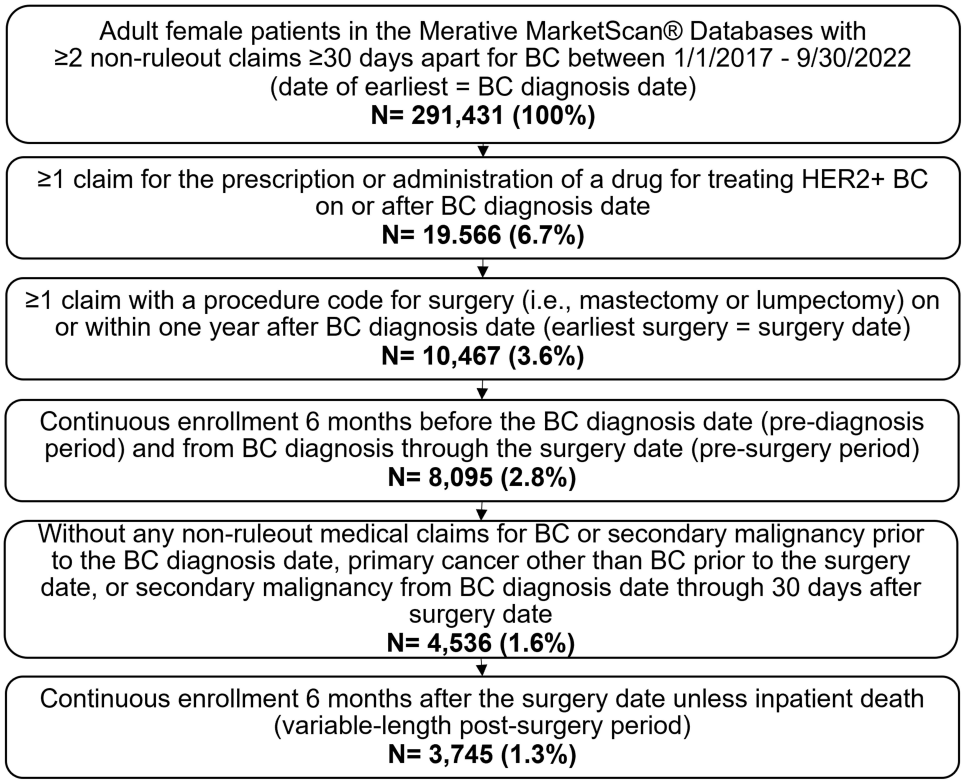

Figure 1 Patient attrition.

except for depression (8.9%, 10.5%, and 7.1%, respectively) and diabetes (8.1%, 10.3%, and 5.7%, respectively). Mean duration of post-surgery follow-up period for the neoadjuvant and post-neoadjuvant, adjuvant only, and surgery only cohorts were 791 days (2.2 years), 838 days (2.3 years), and 908 days (2.5 years), respectively.

Treatment Utilization

Chemotherapy + targeted regimens were the most common in both the neoadjuvant (85.4%) and post-neoadjuvant /adjuvant (52.7%) settings (Table 2). Among patients who received neoadjuvant treatment, chemotherapy + trastuzumab (T) + pertuzumab (P) (77.6%) was the most common regimen. Among those with post-neoadjuvant/adjuvant treatment, the use of chemotherapy + T (43.3%) was common, followed by targeted-only regimens: T alone (14.7%) and T + P (12.1%).

The specific regimens (including chemotherapies used) can be found in Supplemental Table 3a and b. For neoadjuvant treatment (Supplemental Table 3a), carboplatin + docetaxel + trastuzumab (T) + pertuzumab (P) (68.5%) was the most common regimen. For post-neoadjuvant/adjuvant treatment (Supplemental Table 3b), the use of paclitaxel + T (31.5%) was common.

Rates of First Recurrence

During the post-surgery period, the rate of first recurrence was highest in patients with surgery only (70.0%) and slightly higher by nearly 2% in patients with adjuvant treatment only (16.0%) than with neoadjuvant and post-neoadjuvant treatment (14.3%) (Figure 3). The evidence of recurrence was almost equal to that of metastasis and end-of-life care for patients with neoadjuvant and post-neoadjuvant and adjuvant therapy only, but more commonly, additional chemotherapy treatment for the surgery-only cohort. Kaplan Meier curves show median (95% confidence interval) time to first recurrence as 19.45 (13.33, 29.66) months for neoadjuvant and post-neoadjuvant treatment cohort; 20.23 (11.81, 28.30) months for adjuvant only treatment cohort; and 12.32 (8.06, 23.05) months for surgery only cohort (Supplemental Figure 1 and Supplemental Table 4).

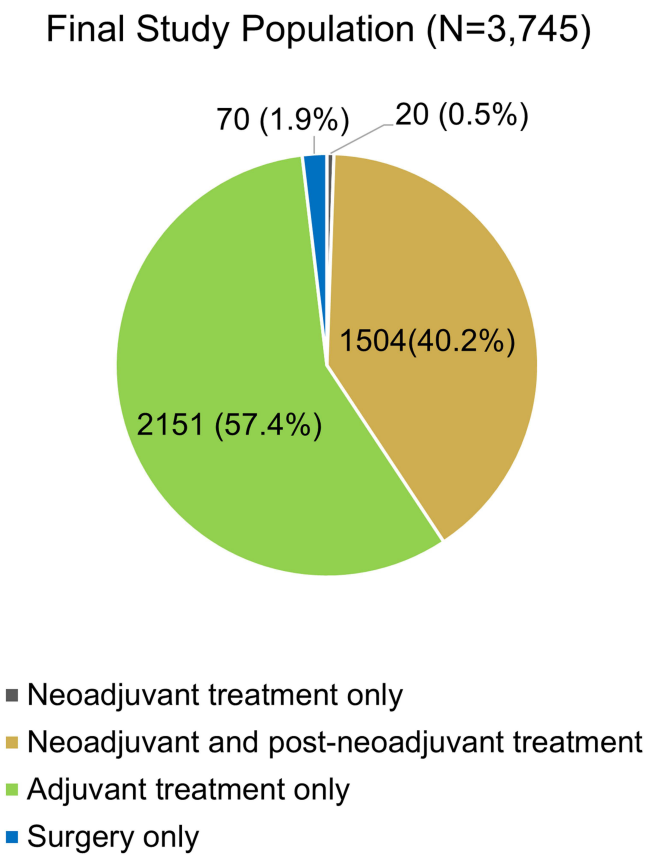

Figure 2 Treatment cohorts.

Impact of Recurrence on HCRU and Cumulative Costs Burden

Among the primary treatment cohorts (neoadjuvant and post-neoadjuvant treatment and adjuvant only, N=3655), 3097 (84.7%) patients had no recurrence, and 558 (15.2%) had recurrence following surgery (436 [78.1%] had the first recurrence within 12 months and 122 [21.9%] had the first recurrence within 12–36 months).

Table 1 Patient Characteristics

	Neoadjuvant and Post-Neoadjuvant (N=1504)	Adjuvant Only (N=2151)	Surgery Only (N=70)
Age, mean (SD)	51.3 (10.6)	55.2 (10.2)	56.5 (12.7)
Insurance plan type, n (%)			
Comprehensive/EPO/PPO	771 (51.3%)	1124 (52.3%)	36 (51.4%)
HMO	227 (15.1%)	349 (16.2%)	20 (28.6%)
POS/CDHP/HDHP/Other	506 (33.6%)	678 (31.5%)	14 (20.0%)
Clinical conditions, n (%)			
Hypertension	334 (22.2%)	615 (28.6%)	22 (31.4%)
Depression	134 (8.9%)	226 (10.5%)	5 (7.1%)
Diabetes (mild/moderate)	121 (8.1%)	221 (10.3%)	4 (5.7%)
Chronic obstructive pulmonary disease	102 (6.8%)	183 (8.5%)	6 (8.6%)
Anemia	63 (4.2%)	99 (4.6%)	8 (11.4%)
Coronary artery disease	28 (1.9%)	60 (2.8%)	4 (5.7%)
Diabetes (with chronic complications)	25 (1.7%)	54 (2.5%)	1 (1.4%)

(*Continued*)

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Table 1 (Continued).

	Neoadjuvant and Post-Neoadjuvant (N=1504)	Adjuvant Only (N=2151)	Surgery Only (N=70)
Days in pre-surgery period, mean (SD)	172 (37)	34 (28)	45 (63)
Days in post-surgery period, mean (SD)	791 (480)	838 (509)	908 (494)

Abbreviations: CDHP, Consumer-driven health plan; EPO, Exclusive provider organization; HDHP, High deductible health plan; HMO, Health maintenance organization; POS, Point of service; PPO, Preferred provider organization.

Table 2 Treatment Regimens

Regimens, n (%)	Neoadjuvant (N=1524)	Post-Neoadjuvant/Adjuvant (N=3655)
Chemo only	**128 (8.4%)**	**129 (3.5%)**
Monotherapy	12 (0.8%)	14 (0.4%)
Combination therapy	116 (7.6%)	115 (3.1%)
Chemo + Targeted	**1302 (85.4%)**	**1928 (52.7%)**
Chemo + T	116 (7.6%)	1581 (43.3%)
Chemo + T + P	1182 (77.6%)	341 (9.3%)
Chemo + Endocrine	**5 (0.3%)**	**2 (0.1%)**
Chemo + Endocrine + Targeted	**16 (1.0%)**	**28 (0.8%)**
Targeted only	**21 (1.4%)**	**1159 (31.7%)**
T	9 (0.6%)	536 (14.7%)
T + P	8 (0.5%)	441 (12.1%)
Ado-trastuzumab emtansine	1 (0.1%)	116 (3.2%)
Endocrine + Targeted	**5 (0.3%)**	**326 (8.9%)**
Endocrine only	**47 (3.1%)**	**83 (2.3%)**
Days in therapy duration, mean (SD)	***128 (33)***	***532 (384)***

Abbreviations: Chemo, Chemotherapy; P, pertuzumab; T, trastuzumab.

HCRU and costs reported for the primary treatment cohorts in the post-surgery period were consistently higher among patients with versus without recurrence (Table 3). Notably, the prevalence of inpatient admissions was two-fold higher among patients with recurrence than among those without recurrence (49% versus 24%), and ER visits were nearly 1.5 times higher (55% versus 38%). These differences were reflected in the costs, with per-patient-per-month (PPPM) inpatient costs being $1557 among those with recurrence versus $641 among those without recurrence. The total PPPM all-cause costs were $15,891 and $13,617, with and without recurrence, respectively.

Compared to all-cause utilization and cost, about half the proportion with an inpatient admission and a third with an ER visit had BC-related utilization in each setting for both with and without recurrence (BC-related IP: 24% and 11% with and without recurrence; BC-related ER visits: 18% and 11% for with and without recurrence). Nearly 90% of the total all-cause costs were BC-related ($13,506 or 85% for with recurrence and $11,985 or 99% without recurrence).

Patients with the first recurrence within 12 months of surgery incurred 31% higher costs in any given month ($p = 0.002$) compared with patients without recurrence; this difference compounds over time (Figure 4). GLM showed that the cumulative cost burden following surgery was higher among patients who experienced the first recurrence within 12 months vs no recurrence ($348,834 vs $265,279). Patients with chemotherapy as a post-neoadjuvant/adjuvant treatment had a higher cumulative cost burden (Risk Ratio [RR] 1.28; $p < 0.001$) compared with patients receiving HER2 targeted treatment in the post-neoadjuvant/adjuvant setting. Patients who received

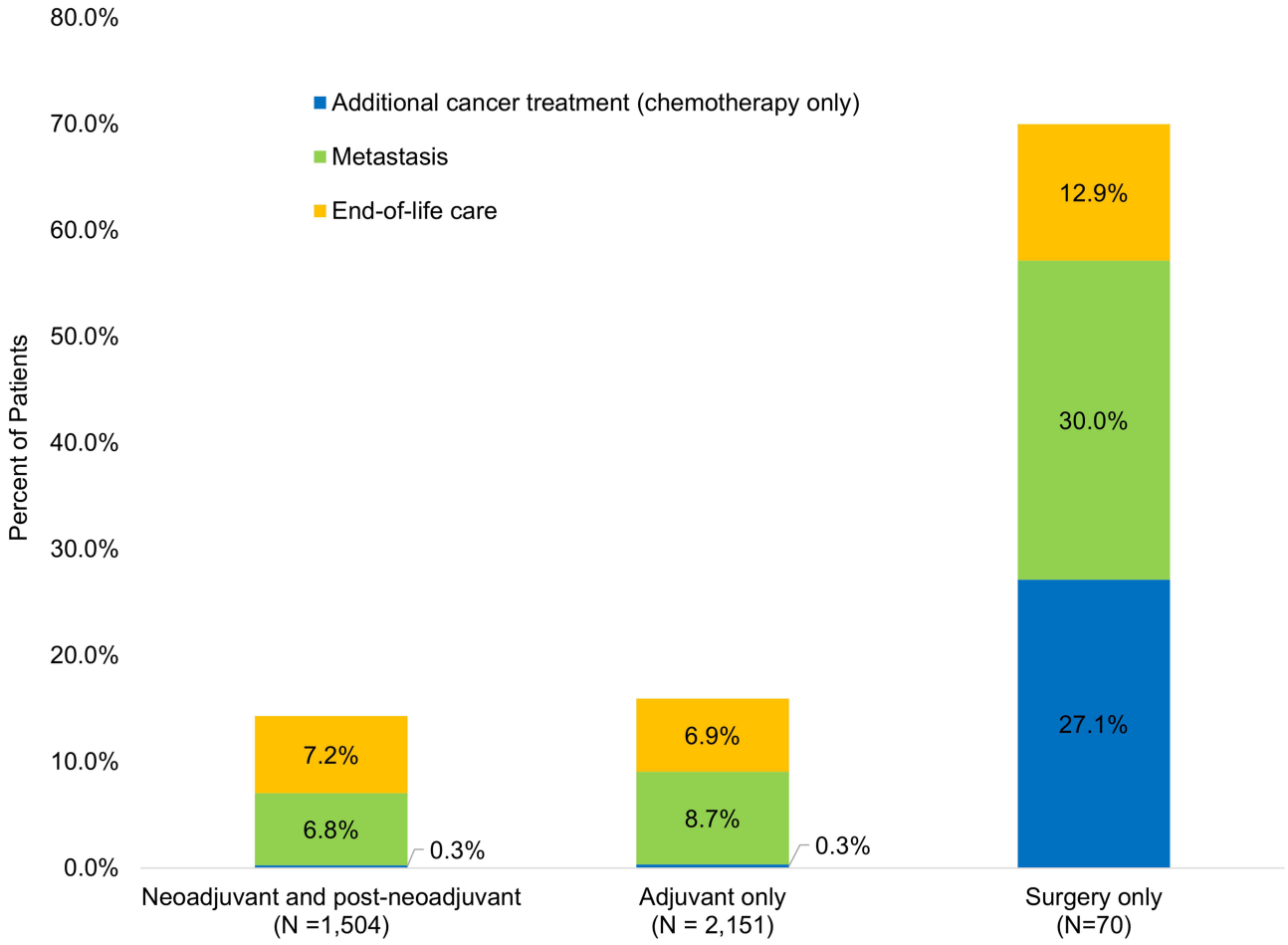

Figure 3 Disease recurrence.

neoadjuvant treatment prior to surgery had a lower cost burden (RR 0.85, p <0.001) compared with patients that did not receive any neoadjuvant therapy.

Similarly, patients with the first recurrence 12–36 months after surgery incurred 44% higher costs in any given month (p < 0.001) compared with patients without recurrence; this difference compounds overtime (Figure 5). GLM showed that the cumulative cost burden following surgery was higher among patients who experienced the first recurrence 12–36 months after surgery vs no recurrence ($376,755 vs $261,688).

Discussion

This retrospective cohort study provides a contemporary assessment of treatment patterns, recurrence rates, and associated cumulative cost burden among patients with HER2+ eBC.

The results presented here are consistent with the published literature but uncover evolving trends in the treatment of HER2+ eBC. The most comparable real-world study by DaCosta Byfield et al used data from the Oncology Management Registry linked with the Optum Research Database from 2008–2013, where 80% of patients received adjuvant therapy only and only 17% received both neoadjuvant and post-neoadjuvant.[11] The current study reported less than 60% with adjuvant therapy only and 40% with both neoadjuvant and post-neoadjuvant, reflecting an increased utilization of neoadjuvant treatment over time. This is likely due to advances in treatment, changes in guidelines, and increased awareness of early systemic intervention for patients with eBC at a higher risk of recurrence.[11]

The rate of first recurrence in the current study was similar to previously published results,[15,21,22] with slightly higher recurrence among patients without neoadjuvant treatment (16.0% versus 14.3%). In particular, metastasis recurrence was

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Table 3 Healthcare Utilization and Costs per Patient per month (PPPM), Post-Surgery Period

	With Recurrence			Without Recurrence		
	All N = 558	**Neoadjuvant and Post-Neoadjuvant Treatment** N = 215	**Adjuvant Only** N = 343	**All** N = 3097	**Neoadjuvant and Post-Neoadjuvant Treatment** N = 1289	**Adjuvant Only** N = 1808
All-cause						
Healthcare Utilization (N, %)						
Inpatient	275 (49.3%)	106 (49.3%)	169 (49.3%)	730 (23.6%)	296 (23.0%)	434 (24.0%)
OP						
ER visit	308 (55.2%)	121 (56.3%)	187 (54.5%)	1182 (38.2%)	449 (34.8%)	733 (40.5%)
OP office visit	558 (100.0%)	215 (100.0%)	343 (100.0%)	3097 (100.0%)	1289 (100.0%)	1808 (100.0%)
Imaging scan	490 (87.8%)	182 (84.7%)	308 (89.8%)	2432 (78.5%)	940 (72.9%)	1492 (82.5%)
OP laboratory service	558 (100.0%)	215 (100.0%)	343 (100.0%)	3097 (100.0%)	1289 (100.0%)	1808 (100.0%)
OP office-administered systemic treatment	555 (99.5%)	212 (98.6%)	343 (100.0%)	3087 (99.7%)	1280 (99.3%)	1807 (99.9%)
OP pharmacy	553 (99.1%)	213 (99.1%)	340 (99.1%)	3063 (98.9%)	1276 (99.0%)	1787 (98.8%)
PPPM Healthcare Costs (Mean, SD)						
Inpatient	$1557 ($4033)	$1515 ($3868)	$1583 ($4139)	$641 ($2489)	$738 ($2540)	$571 ($2451)
OP	$13,799 ($10,967)	$13,975 ($11,535)	$13,689 ($10,612)	$12,550 ($10,725)	$12,329 ($11,539)	$12,708 ($10,106)
ER visit	$74 ($182)	$73 ($169)	$76 ($191)	$56 ($354)	$40 ($121)	$68 ($452)
OP office visit	$282 ($223)	$264 ($208)	$293 ($232)	$246 ($221)	$213 ($226)	$269 ($215)
Imaging scan	$183 ($343)	$217 ($415)	$163 ($287)	$81 ($166)	$82 ($162)	$81 ($169)
Laboratory service	$429 ($1245)	$458 ($1817)	$410 ($677)	$391 ($1100)	$363 ($1276)	$411 ($955)
OP office-administered systemic treatment	$7559 ($7761)	$7902 ($8413)	$7345 ($7326)	$6842 ($7365)	$7167 ($8189)	$6610 ($6709)
Other OP service	$5272 ($4416)	$5061 ($4382)	$5404 ($4438)	$4934 ($4649)	$4464 ($4805)	$5269 ($4507)
OP pharmacy	$534 ($1186)	$564 ($1253)	$516 ($1143)	$426 ($1333)	$420 ($1262)	$430 ($1382)
Total medical (Inpatient + OP)	$15,357 ($12,285)	$15,491 ($12,417)	$15,273 ($12,220)	$13,191 ($11,267)	$13,067 ($12,213)	$13,279 ($10,544)
Total (Total medical + OP pharmacy)	**$15,891 ($12,392)**	**$16,054 ($12,392)**	**$15,789 ($12,409)**	**$13,617 ($11,321)**	**$13,487 ($12,260)**	**$13,710 ($10,602)**
BC-related						
Healthcare Utilization (N, %)						
Inpatient	135 (24.2%)	59 (27.4%)	76 (22.2%)	333 (10.8%)	156 (12.1%)	177 (9.8%)
OP						
ER visit	102 (18.3%)	40 (18.6%)	62 (18.1%)	344 (11.1%)	92 (7.1%)	252 (13.9%)
OP office visit	558 (100.0%)	215 (100.0%)	343 (100.0%)	3072 (99.2%)	1275 (98.9%)	1797 (99.4%)
Imaging scan	490 (87.8%)	182 (84.7%)	308 (89.8%)	2432 (78.5%)	940 (72.9%)	1492 (82.5%)
OP laboratory service	557 (99.8%)	214 (99.5%)	343 (100.0%)	3092 (99.8%)	1285 (99.7%)	1807 (99.9%)
OP office-administered systemic treatment	555 (99.5%)	212 (98.6%)	343 (100.0%)	3087 (99.7%)	1280 (99.3%)	1807 (99.9%)

OP pharmacy	385 (69.0%)	154 (71.6%)	231 (67.4%)	2155 (69.6%)	848 (65.8%)	1307 (72.3%)
PPPM Healthcare Costs (Mean, SD)						
Inpatient	$640 ($1887)	$715 ($1972)	$593 ($1832)	$313 ($1656)	$367 ($1588)	$275 ($1702)
OP	$12,599 ($10,579)	$12,864 ($11,322)	$12,434 ($10,099)	$11,493 ($10,154)	$11,201 ($10,721)	$11,701 ($9,727)
ER visit	$19 ($80)	$18 ($80)	$19 ($80)	$22 ($335)	$7 ($51)	$34 ($436)
OP office visit	$195 ($184)	$180 ($172)	$205 ($190)	$172 ($197)	$141 ($198)	$195 ($192)
Imaging scan	$183 ($343)	$217 ($415)	$163 ($287)	$81 ($166)	$82 ($162)	$81 ($169)
Laboratory service	$359 ($1164)	$383 ($1707)	$344 ($617)	$335 ($1085)	$302 ($1256)	$359 ($944)
OP office-administered systemic treatment	$7559 ($7761)	$7902 ($8413)	$7345 ($7326)	$6842 ($7365)	$7167 ($8189)	$6610 ($6709)
Other OP service	$4284 ($4019)	$4164 ($4161)	$4359 ($3931)	$4039 ($4051)	$3502 ($3797)	$4422 ($4182)
OP pharmacy	$267 ($979)	$346 ($1151)	$217 ($853)	$180 ($1007)	$215 ($1047)	$155 ($977)
Total medical (Inpatient + OP)	$13,239 ($10,925)	$13,579 ($11,563)	$13,026 ($10,518)	$11,806 ($10,394)	$11,568 ($11,021)	$11,975 ($9923)
Total (Total medical + OP pharmacy)	**$13,506 ($10,961)**	**$13,925 ($11,547)**	**$13,244 ($10,585)**	**$11,985 ($10,403)**	**$11,782 ($11,050)**	**$12,130 ($9917)**

Abbreviations: ER, emergency room; IP, inpatient; OP, outpatient; PPPM, per patient per month.

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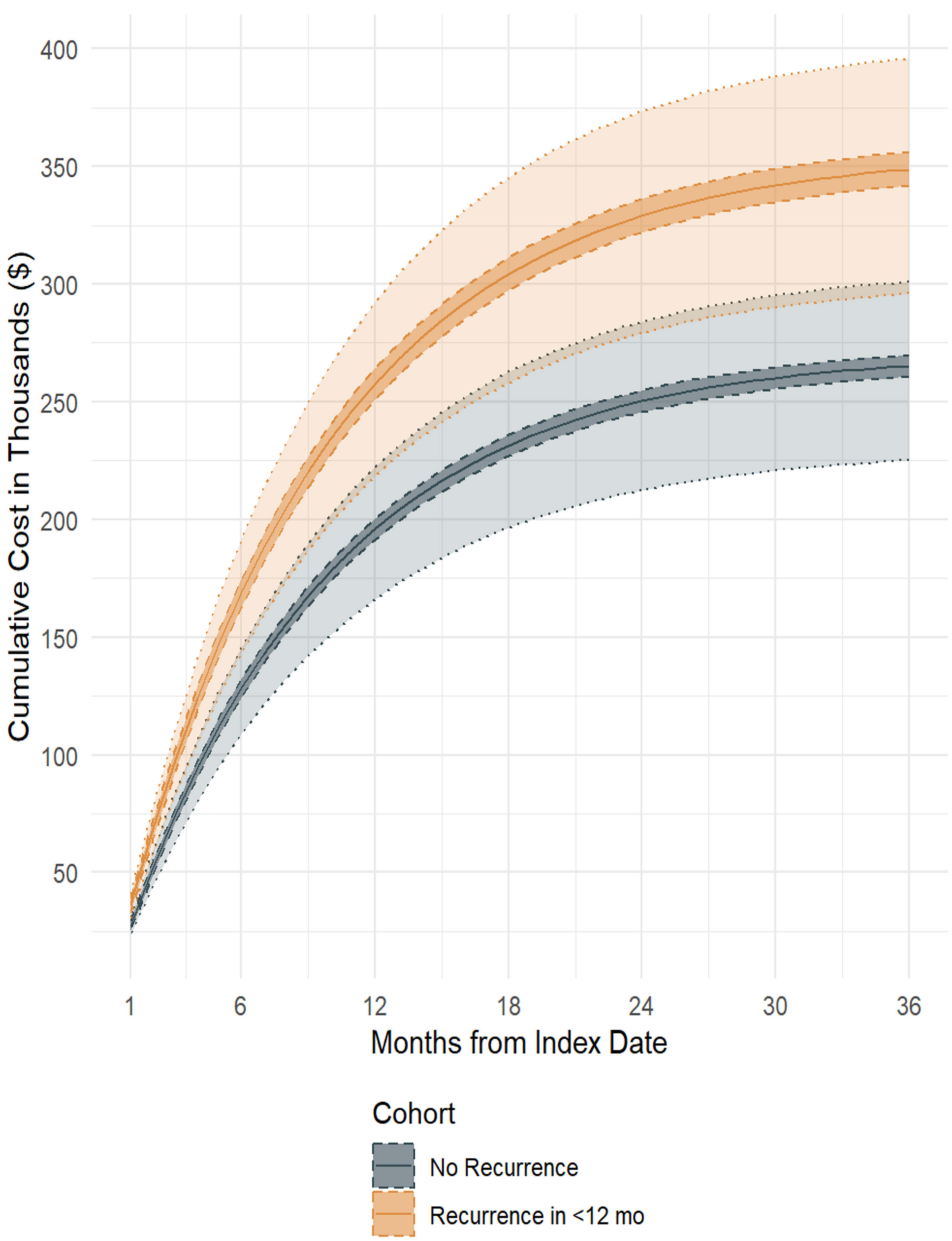

Figure 4 GLM cumulative cost comparing no recurrence versus recurrence within 12 months of surgery. Among patients with neoadjuvant and post-neoadjuvant treatment and adjuvant treatment only (N=3655), of which 3097 with no recurrence and 436 with recurrence within 12 months of surgery. Mean (middle line), IQR (darkly shaded band), and 95% CI of mean (lightly shaded band) are shown in the figure.

higher among patients not treated with systemic therapy (30.0% in the surgery-only group and 8.7% in the adjuvant-only group, compared to 6.8% in neoadjuvant and post-neoadjuvant). A recent study among patients with high-risk HER2+ eBC where 7.0% were diagnosed with metastasis during follow-up, but when stratified by neoadjuvant therapy, metastasis was present in only 4.6% with neoadjuvant therapy versus 10.9% without.[12] These differences in the rate of the first recurrence observed in this study and previously stresses the critical importance of performing comprehensive clinical staging at the time of eBC diagnosis and selection of systemic treatment intervention according to the guidelines in the neoadjuvant and adjuvant settings.

Healthcare utilization and associated costs are high among patients with HER2+ eBC, and are higher in patients with recurrence. When the descriptive per-month costs in the current study were extrapolated to 12 months, the total all-cause costs in the year following surgery were $163,406 without recurrence and $190,691 with recurrence, which is

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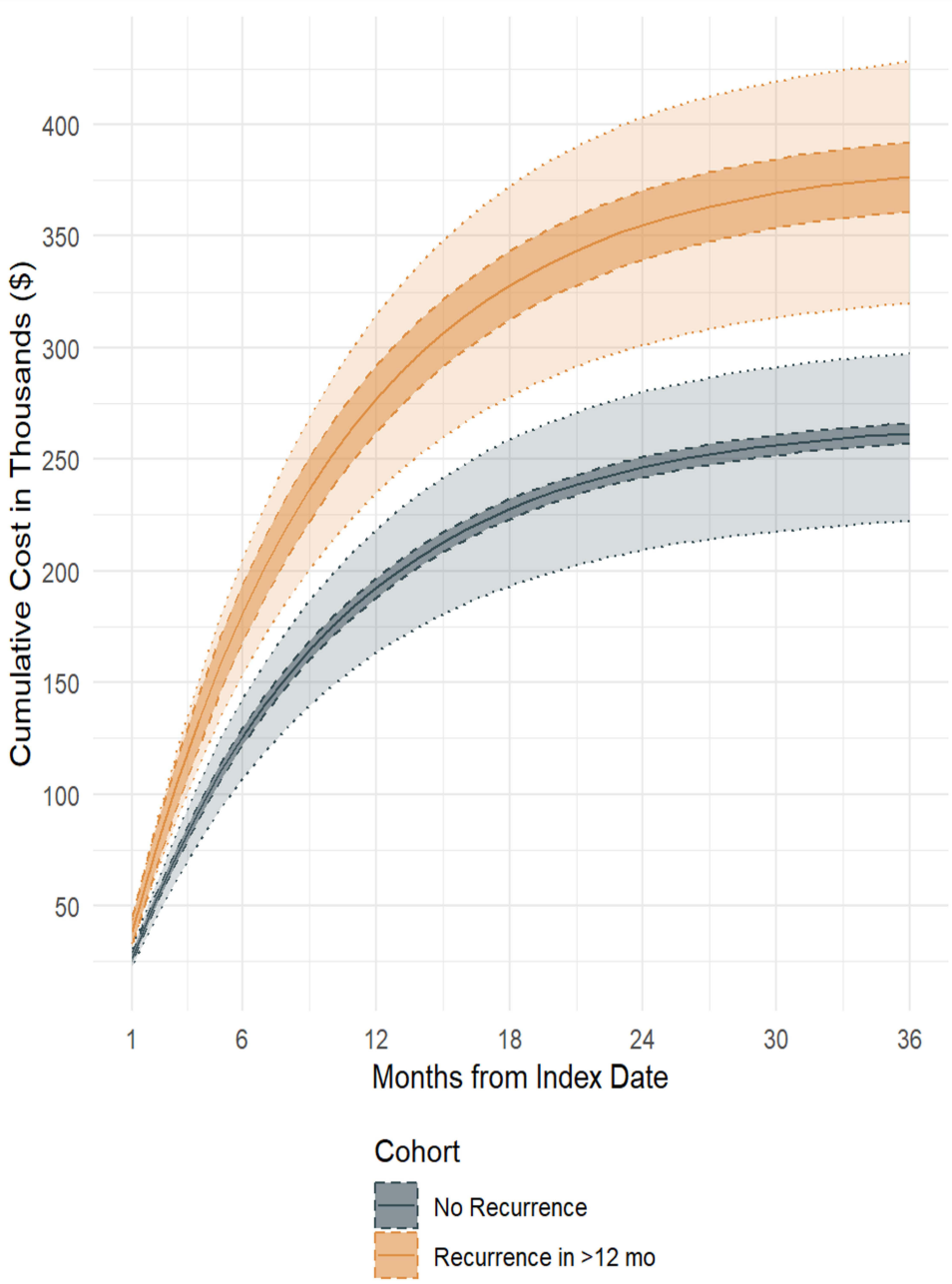

Figure 5 GLM cumulative cost comparing no recurrence versus recurrence 12–36 months after surgery. Among patients with neoadjuvant and post-neoadjuvant treatment and adjuvant treatment only (N=3655), of which 3097 with no recurrence and 122 with recurrence 12–36 months after surgery. Mean (middle line), IQR (darkly shaded band), and 95% CI of mean (lightly shaded band) are shown in the figure.

comparable to the $176,779 reported by DaCosta Byfield et al during the first 12 months of initial treatment.[11] The focus of the current study, however, was the cumulative cost burden observed between patients with HER2+ eBC with and without recurrence, which is a new contribution to the literature.

The results presented here underline the higher cumulative cost burden among patients with recurrence compared to patients without recurrence, particularly for those with early recurrence. The slightly higher cost difference among those with the first recurrence at 12–36 months (▲$115,067) versus <12 months (▲$83,555) is somewhat counter to what has been observed in patients with metastatic disease, where early recurrence has greater cumulative costs compared to delayed recurrence.[17] But follow-up in the current study was limited (all within 36 months) and so neither <12 or 12–36 month time periods should be considered delayed; thus, both periods provided evidence of an increased cost burden with

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early recurrence. Additionally, upon further investigation, first recurrence at 12–36 months was associated with more metastatic cases; the reason for the first recurrence being metastasis was more likely at 12–36 months (64.1%) compared to <12 months (48.9%). Metastatic breast cancer is known to be costly[23] and so likely contributes to the increased cumulative cost in the 12–36 months ($376,755) versus <12 months ($348,834).

These findings highlight the unmet needs of the initial recurrence within 3-years of eBC diagnosis and the associated cumulative cost burden, emphasizing the importance of early intervention and newer HER2 targeted therapy. Currently, the novel antibody drug conjugate (ADC), trastuzumab deruxtecan, is being trialed for specific BC patient populations. The DESTINY-Breast11 (DB-11) clinical trial is currently examining the effectiveness of neoadjuvant trastuzumab deruxtecan against other treatments among patients with high-risk HER2+ eBC.[13] The DESINTY-Breast05 (DB-05) clinical trial is also exploring the effectiveness of trastuzumab deruxtecan but against trastuzumab emtansine among patients with high-risk HER2+ primary BC who do not achieve complete response after appropriate neoadjuvant therapy.[14]

Utilization of neoadjuvant treatment has shown to be both clinically and economically effective. One modeling study demonstrated that treatment with currently available antibody-drug conjugate treatments yielded lower costs, longer life, and better quality of life, some of which was a result of being less likely to experience recurrence.[24] A cost effectiveness analysis integrating metrics in toxicity, effectiveness, and costs found that neoadjuvant treatment regimens comprising trastuzumab followed by tailored post-operative therapy reduced treatment costs compared to more intensive chemotherapy regimens, with all strategies yielding nearly identical long-term rates of estimated cancer recurrence risk.[25] The association of neoadjuvant therapy with lower costs and post-neoadjuvant/adjuvant chemotherapy with higher costs (compared to adjuvant HER2 targeted therapy) reported in the current study highlights the importance of treating patients with HER2+ eBC concordantly per the guidelines.[4,18]

Early recurrence in patients with HER2+ eBC has been a significant concern and can contribute to roughly $100k in additional healthcare costs over a 3-year period. While advances in targeted therapies have improved outcomes, recurrence due to metastasis remains a concern, emphasizing the need for early intervention and new therapies.

Limitations

The limitations of this study include those inherent to any retrospective analysis. First, the analysis was limited to only those individuals with commercial health coverage or private Medicare coverage. Consequently, the results of this analysis may not be generalizable to patients with HER2+ eBC with other insurance or without health insurance coverage. Second, the potential for misclassification of HER2+ eBC, covariates, or study outcomes was present, as patients were identified through administrative claims data, as opposed to medical records. In the absence of clinical data, a proxy algorithm was used to identify HER2+ subtype and disease recurrence. Since HER2+ is identified based on the utilization of HER2 targeted treatment at any time, this may limit the generalizability of treatment patterns. While defining recurrence lacked the benefit of clinical data, a systematic review estimating breast cancer recurrence in administrative claims found high accuracy (93%) among the majority rule based (59%) algorithms,[26] similar to the one used in the current study. Furthermore, clinical data would be essential to determine the HR subtypes (positive vs negative) and clinical staging of BC (TNM), which are known to have variable impacts on recurrence and treatment selection. In addition, there may be systematic differences between the study subcohorts with and without recurrence (eg, differences in TNM staging) that account for the descriptive differences found in healthcare costs and HCRU. While the modeling controlled for variables such as patient demographics, and treatment type received, certain unobserved confounding variables are likely to impact the outcome estimates (eg, risk assessment at eBC diagnosis and HR status). Further research is warranted to confirm the findings of the current study by using robust clinical data linked to payer claims data.

Conclusion

The majority of patients received neoadjuvant and post-neoadjuvant treatment or adjuvant only treatment. However, for patients who were not treated with antineoplastic pharmacologic therapy in neoadjuvant or adjuvant settings (before or after breast cancer surgery), the rate of first disease recurrence was highest. Among the primary treatment cohorts, data

revealed that patients with HER2+ eBC who experienced recurrence incurred a significantly higher cost burden than those without recurrence. Specifically, the 3-year cumulative cost burden was higher among patients with early recurrence compared to those with no recurrence during follow-up, and increased further among patients with chemotherapy in the adjuvant setting (vs HER2 targeted treatment) and among those without any neoadjuvant therapy prior to surgery. The study findings highlight that the use of a more effective HER2 targeted treatment that delays the time of first recurrence in the neoadjuvant and adjuvant settings may improve patient outcomes and reduce the long-term healthcare burden associated with BC.

Data Sharing Statement

Data supporting the findings of this study are available from Merative. Restrictions apply to the availability of these data, which were used under the license of this study.

Ethics Approval and Informed Consent

All database records were statistically de-identified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, it was exempted from Institutional Review Board approval.

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Disclosure

SM and EF are employed by Daiichi Sankyo, Inc and own stock options in Daiichi Sankyo, Inc. NP, MM, and CH are employed by Merative which received funding from Daiichi Sankyo, Inc. to conduct this study. This research was presented in part at the 2024 AMCP Nexus Conference in Las Vegas, Nevada. Dr Eleanor Faherty was an employee 2019-2023 of Astra Zeneca.

The authors report no other conflicts of interest in this work.

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