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An evaluation of the healthcare costs of metastatic breast cancer

A retrospective matched cohort study

Hsuan-Ming Chen, MS[a], Jin-Hua Chen, PhD[b,c], Shao-Chin Chiang, PharmD[d], Yi-Chun Lin, MS[b], Yu Ko, PhD[a,e,*]

Abstract

To determine the economic burden of metastatic breast cancer (MBC) in Taiwan, we conducted a national retrospective claim database analysis to evaluate the incremental healthcare costs and utilization of MBC patients as compared to their breast cancer (BC) and breast cancer free (BCF) counterparts.

Data were obtained from the National Health Insurance Claim Database and the Taiwan Cancer Registry database between 2012 and 2015. All healthcare utilization and costs were calculated on a per-patient-per-month (PPPM) basis and were compared among groups using the generalized linear model adjusting for age group, residential area, and Charlson comorbidity index group.

A total of 1,606 MBC patients were matched to 6,424 BC patients and 6,424 BCF patients. The majority of overall MBC healthcare costs were attributed to outpatient costs (75.1%), followed by inpatient (23.2%) and emergency room costs (1.7%). The PPPM total healthcare costs of the MBC, BC, and BCF groups were TWD 7,422, 14,425, and 2,114, respectively. The adjusted PPPM total healthcare cost ratio of MBC to BCF was 4.1. Compared to BCF patients, the patients receiving both human epidermal growth factor receptor 2-targeted therapy and endocrine therapy incurred 28.1 times PPPM total costs. The adjusted PPPM total healthcare cost ratio of recurrent MBC to BCF was 2.3, while the ratio was 12.2 in the de novo MBC group.

Patients with MBC are associated with substantial economic burden, particularly in outpatient costs. The study findings could be useful for MBC-related economic evaluations and health resource allocation.

Abbreviations: BC = breast cancer, BCF = breast cancer free, CCI = Charlson Comorbidity Index, ER = emergency room, HER2 = human epidermal growth factor receptor 2, MBC = metastatic breast cancer, NHCD = National Health Insurance Claim Database, NHI = National Health Insurance, PPPM = per-patient-per-month, TCDB = Taiwan cancer database, TWD = Taiwan Dollar.

Keywords: claim data analysis, cost analysis, cost of illness, health expenditures, matched cohort analysis, metastatic breast cancer

1. Introduction

Breast cancer (BC) is the second most common cancer in both sexes combined and the most common cancer in women. An estimated 1.67 million women worldwide were diagnosed with BC in 2012, with almost 52% of the cases (883,000) occurring in more developed regions.[1] Approximately 6 percent of BC patients had simultaneous metastatic disease identified at the time of initial diagnosis between 2008 and 2014.[2] In Taiwan, one in 100 women has BC, and the prevalence has been estimated at 115,045 in women and 386 in men in 2013.[3] According to the Taiwan Cancer Registry Report in 2018 it is estimated that 16,265 women were newly diagnosed with BC, with a total of 1,113 new de novo metastatic cases that accounted for 6.84% of all new BC diagnoses.[4]

The treatment regimens for metastatic breast cancer (MBC) are continually developing as a result of the invention of new drugs and new technologies. There are 4 treatment options for MBC, which include surgery, radiotherapy, systemic therapy, and palliative care. In general, for women with MBC, systemic (drug) therapies are the main treatments. The systemic drugs for MBC are prescribed based on a patient's hormone receptor status and human epidermal growth factor receptor 2 (HER2) status. Specifically, the pharmaceutical management includes chemotherapy, hormone therapy, and targeted therapy. Patients with hormone receptor-positive BC must have hormone therapy, whereas patients with HER2-positive BC can prolong their

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[a] Department of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan, [b] Statistics Center, Office of Data Science, Taipei Medical University, Taipei, Taiwan, [c] Graduate Institute of Data Science, College of Management, Taipei Medical University, Taipei, Taiwan, [d] Department of Pharmacy, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan, [e] Research Center of Pharmacoeconomics, College of Pharmacy, Taipei Medical University, Taipei, Taiwan.

[*] Correspondence: Yu Ko, Department of Pharmacy, College of Pharmacy, Taipei Medical University, No.250, Wuxing St., Taipei 11031, Taiwan (e-mail: nancyko@tmu.edu.tw).

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overall survival with targeted therapy, and chemotherapy can be used for any phenotype of MBC. With the continuous advancement of technology, the high cost of these new treatments make MBC a substantial medical burden globally. Montero et al performed an evaluation to quantify the economic burden of MBC, taking the US managed care perspective. The mean total direct medical costs were estimated at $9,788 per patient per month (PPPM), ranging from $5,303 (endocrine therapy) to $13,926 (non-systemic therapy).[5] Moreover, several studies reported the medical costs of various phenotypes of MBC, such as HER2 positive patients ($11,107 per month),[6] hormone receptor positive patients ($87,638 per year),[7] and hormone receptor positive/HER2 negative patients ($11,334 per month).[8]

In Taiwan, there were 142,483 women who sought medical advice for BC in 2019. In addition, the National Health Insurance Administration within the Ministry of Health and Welfare reported that the disbursement for BC was 15.1 billion Taiwan Dollar (TWD) in 2019, with an average 5-year growth rate of 8.5%, which was the second highest among cancers.[9] Nevertheless, there has been no study that specifically examines the costs of MBC. The aims of this study were to evaluate various types of healthcare costs and utilization of patients with MBC and to compare various types of medical costs among different therapeutic subgroups of patients with MBC. It is hoped that our research will be useful for healthcare resource allocation and will also provide essential data for future local economic evaluations.

2. Methods

We conducted a retrospective, matched cohort study to assess the incremental healthcare costs and utilization of all adults with MBC as compared to their BC and breast cancer-free (BCF) counterparts in Taiwan. This study was approved by Taipei Medical University- Joint Institutional Review Board (Approval number: N201709052).

2.1. Data sources

Data were obtained from the Health and Welfare Data Science Center, Ministry of Health and Welfare, a large data repository site that preserves, manages, and analyzes health data. Data on healthcare utilization and costs from 2012 through 2015 were extracted from the National Health Insurance Claim Database (NHCD) and the National Cancer Registry Database. In 1995, the Taiwanese government launched a single-payer National Health Insurance (NHI) program, which covered 99.6% of the 23 million Taiwanese residents in 2017. The NHI collects information about patients' demographics, inpatient and outpatient visits and orders, medication prescriptions, and enrollment history. In addition, patients' utilization of medical services, including the date, place, and type of service, is recorded. Diagnoses were coded by the Ninth Revision Clinical Modification Codes (ICD-9-CM) while medication prescriptions were coded according to the NHI program medication classification system. Our study used the full-population files of the NHCD, which contain all beneficiaries in the NHI program.

The Taiwan National Cancer Registry program is a population-based cancer registry plan that was instituted in Taiwan in 1979. All hospitals with ≥ 50 beds that provide outpatient and/or hospitalized cancer care are enrolled, and they are required to report all newly diagnosed malignant neoplasms to the registry. Currently, ten major medical centers, 1 comprehensive cancer hospital, and hundreds of regional and district general hospitals are actively involved in cancer diagnosis and treatment. The Taiwan Cancer Database (TCDB), which accounts for the registration of 90% of all major cancers, collects patients' information about the American Joint Committee on Cancer staging, date of initial diagnosis, primary cancer site, demographics, clinical tumor, node, metastasis staging, pathological tumor, node, metastasis staging, metastasis, surgical procedures, chemotherapy, radiotherapy, etc.

2.2. Sample selection

The enrollment period of this study was between January 1st and December 31st, 2012. The patients with a new diagnosis of MBC or BC during the enrollment period were identified as a new case in the MBC group or BC group, respectively. For each new case, the first date of the MBC or BC diagnosis was defined as the index date. In addition, each patient in the BCF group was randomly assigned an index date in 2012. A 1-year window was employed to capture all comorbidities prior to the index date.

Patients with MBC were identified in 2 ways: (1) those with a new diagnosis of primary BC (ICD-O-3: 50.x) and stage IV cancer in the TCDB during the enrollment period; and (2) those with a diagnosis of primary BC (ICD-O-3: 50.x) in the TCDB and 1 or more NHCD claims with a diagnosis of distant secondary and unspecified malignant neoplasm of lymph nodes (ICD-9-CM code 196.XX), respiratory and digestive systems (ICD-9-CM: code 197.XX), and/or other specified sites (ICD-9-CM: code 198.XX) during the enrollment period.[5,6,10,11] These MBC patients were then further classified into 2 categories: (1) de novo MBC: BC was already metastatic at first diagnosis, and (2) recurrent MBC: BC progressed to metastatic from an earlier stage. De novo MBC patients were those with either stage IV recorded in the TCDB or whose first diagnosis of metastasis (i.e., the index date) recorded in the NHCD fell within 90 days after the diagnosis of BC. Recurrent MBC patients were those whose index date was more than 90 days after their diagnosis of BC as recorded in the NHCD. In addition, we restricted the study population to adults (i.e., aged 20 years or older on the index date), and in order to ensure that information about diagnosis and outcomes were complete, patients had to be continuously enrolled in the health plan for at least 90 days after the index date.[5] In order to exclude patients with multiple primary cancers or regional cancer metastases, the MBC patients identified were excluded if they met the following criteria: (1) had a primary cancer site other than breast as recorded in the TCDB, or (2) had a diagnosis of secondary malignancy of breast (ICD-9-CM code: 198.81) or secondary malignancy neoplasm of axilla and upper limb nodes (ICD-9-CM code: 196.3).

To account for confounding biases, the identified MBC patients were matched with BC and BCF patients on a 1:4:4 basis by age, residential region (divided into northern, central, southern, and eastern districts of Taiwan according to beneficiaries' registered residence zip code), and Charlson Comorbidity Index (CCI).[12] The 1:4:4 ratios were chosen in order to increase statistical power and also because increasing the number of controls beyond 5 brings rapidly diminishing returns.[13] The identified MBC patients that could only be matched with 3 or fewer controls were excluded.

2.3. Subgroup classification

Subgroup classification and comparisons were made in this study. In addition to dividing MBC patients into de novo and recurrent

groups, we also classified them based on their initial type of systemic therapy after the index date:

(1) Endocrine therapy: Patients who received tamoxifen, toremifene, anastrozole, letrozole, exemestane, goserelin, or megestrol acetate were classified in the endocrine therapy subgroup; these patients were likely to have hormone receptor positive and HER2 negative MBC.
(2) HER2 targeted therapy: Patients who received lapatinib or trastuzumab alone were classified in this subgroup; these patients were likely to have hormone receptor negative and HER2 positive MBC.
(3) Concomitant HER2 targeted therapy and endocrine therapy, a subset of the HER2 targeted therapy group: patients who were treated with HER2 targeted therapy and endocrine therapy; these patients were likely to have hormone receptor positive and HER2 positive MBC.
(4) Cytotoxic chemotherapy or no systemic therapy: This group of patients did not receive any HER2 therapy or endocrine therapy; instead they may have received surgery, radiation, or chemotherapy. These patients were likely to have triple negative MBC.

Moreover, MBC patients were divided into those with progression and those without. Due to the restrictions of the NHCD, progression of MBC was defined as a change in treatment regimen, that is, adding a new anti-BC drug that had not been used previously, except where aromatase inhibitors were added for chemotherapy-induced amenorrhea.[10,14] Nevertheless, if a new drug was added to a regimen and it conformed to the National Comprehensive Cancer Network guidelines, it was considered an addition to the existing line, rather than changing to a new line of therapy as a result of progression. Moreover, using chemotherapy before endocrine therapy was not considered disease progression.

2.4. Outcome measures

All healthcare utilization and costs were calculated on PPPM basis since the index date, and the differences among BCF, BC, and MBC groups were examined. Healthcare utilization included the number of inpatient admissions, outpatient visits, and emergency room (ER) visits while healthcare costs included total inpatient costs, total outpatient costs, total ER costs, outpatient medication costs, inpatient medication costs, and ER medication costs.

2.5. Statistical analysis

All study variables were presented as descriptive statistics for the 3 study groups and also for each of the subgroups. Demographic characteristics of the study sample were presented by frequencies and percentages for categorical variables and by mean and standard deviation for continuous variables. To make group comparisons after matching, analysis of variance was used for continuous variables (e.g., age), the Kruskal-Wallis test was used for continuous but non-normally distributed variables (e.g., CCI score), and the Chi-square test was performed for categorical variables (e.g., gender and region). Healthcare costs and utilization were estimated for each patient on a monthly basis from the index date until the end of follow-up (i.e., death or December 31, 2015, whichever came first). Potential biases associated with censored data were minimized by partitioning the time periods into monthly intervals. The right-skewed healthcare costs were compared among groups using the Kruskal-Wallis test and the generalized linear model with a gamma distribution and a log link. In addition, healthcare utilization was compared among groups by the Kruskal-Wallis test and the generalized linear model with a negative binomial distribution and log link function. All of the generalized linear models were adjusted for age group, residential area, and CCI group.

In Taiwan's global budget payment scheme, each treatment is assigned a certain number of points that reflects relative values in a point schedule. The point value is usually close to TWD 1, though it varies by quarter (i.e., every 3 months) and health service category. For ease of calculation and interpretation, the points were converted to monetary values by assigning TWD 1 for each point. All data analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). A 2 tailed *P*-value $< .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study sample

A total of 288 new cases of de novo MBC and 1,318 new cases of recurrent MBC were identified. These 1,606 MBC patients were matched to 6,424 BC patients and 6,424 BCF patients. The matching was successful, as all covariates used in matching were not significantly different among the 3 groups (all $p > .05$). As shown in Table 1, all of the MBC patients were female (100%) and many were ages 41 to 50 years old (36.1%). A majority of them lived in the northern regions of Taiwan (55.2%), had a CCI score of zero (83.1%), and were progression-free (89.9%). Moreover, approximately half had received endocrine therapy. Compared with BC patients, the MBC group had a significantly lower rate of receiving HER2 targeted therapy and/or endocrine therapy.

3.2. Monthly healthcare costs and utilization

As presented in Table 2, the majority of overall MBC healthcare costs were attributed to outpatient costs (75.1%), followed by inpatient (23.2%) and ER costs (1.7%), with a mean monthly cost of TWD 5,574, TWD 1,725, and TWD 124, respectively. The mean monthly total healthcare cost was TWD 2,114 PPPM in BCF patients and TWD 14,425 PPPM in BC patients. Multivariate analysis showed that, compared to BCF patients, MBC patients incurred 4.08 times monthly total costs, 4.72 times monthly outpatient costs, 1.60 times inpatient costs, and 1.65 times ER costs (all $P < .05$) (Table 3). In addition, after adjusting for age, residential area, and CCI score, the generalized linear model showed that the mean numbers of PPPM outpatient visits, inpatient visits, and ER visits were significantly higher in MBC patients than in BCF patients, with ratios ranging from 1.57 in ER visits to 11.70 in inpatient visits (all $P < .05$). Moreover, the BC patients had greater PPPM healthcare utilization than the other 2 groups, with an average of 0.13/2.70/0.03 inpatient/outpatient/ER visits per month, compared to 0.03/2.17/0.03 visits in the MBC group and 0.01/1.3/0.02 visits in the BCF group.

3.3. Subgroup analysis

Subgroup analyses were performed using the generalized linear models.

Table 1

Characteristics of MBC, BC, and BCF patients after matching.

	BCF (n = 6,424)		BC (n = 6,424)		MBC (n = 1,606)	
	n	%	n	%	n	%
Gender						
Female	6,424	100.0	6,424	100.0	1,606	100.0
Age						
20–30	56	0.9	56	0.9	14	0.9
31–40	716	11.1	716	11.1	179	11.1
41–50	2,316	36.1	2,316	36.1	579	36.1
51–60	1,960	30.5	1,960	30.5	490	30.5
61–70	976	15.2	976	15.2	244	15.2
71–80	328	5.1	328	5.1	82	5.1
>=81	72	1.1	72	1.1	18	1.1
Mean (SD), yr	52.4 (10.6)		52.4 (10.6)		52.4 (10.6)	
CCI score						
0	5,344	83.1	5,344	83.1	1,336	83.1
1	832	13.0	832	13.0	208	13.0
>=2	248	3.9	248	3.9	62	3.9
Mean (SD), points	0.21 (0.49)		0.21 (0.49)		0.21 (0.49)	
Residential area						
Central	1,324	20.6	1,324	20.6	331	20.6
East	52	0.8	52	0.8	13	0.8
North	3,548	55.2	3,548	55.2	887	55.2
South	1,528	23.8	1,528	23.8	382	23.8
Treatment						
HER2 (+) & HR (−)			432	6.7	53	3.3
HER2 (+) & HR (+)			229	3.6	34	2.1
HER2 (−) & HR (+)			4,447	69.2	789	49.1
HER2 (−) & HR (−)			1,316	20.5	730	45.3
MBC Type						
De novo MBC					288	18.0
Recurrent MBC					1,318	82.0
Disease status						
Progression					163	10.1
Progression-free					1,440	89.9

BC = breast cancer, BCF = breast cancer free, CCI = Charlson Comorbidity Index, HER2 = human epidermal growth factor receptor 2, MBC = metastatic breast cancer.

Table 2

Unadjusted monthly healthcare costs and utilization of MBC, BC, and BCF patients.

	BCF (n = 6,424)		BC (n = 6,424)		MBC (n = 1,606)		
	TWD	%	TWD	%	TWD	%	*P*-value
Total healthcare costs							
Mean (SD)	2,114 (7,090)	100.0	14,425 (15,416)	100.0	7,422 (16,628)	100.0	<.0001
Median (IQR)	1,527 (707)		9,759 (9,935)		4,529 (2,420)		
Total inpatient costs							
Mean (SD)	719 (5,114)	34.0	4,530 (9,015)	31.4	1,725 (8,473)	23.2	<.0001
Median (IQR)	0 (0)		1,845 (3,275)		0 (947)		
Inpatient drug costs							
Mean (SD)	119 (1,849)	5.7	1,676 (5,003)	11.6	347 (1,916)	4.7	<.0001
Median (IQR)	0 (0)		44 (1,194)		0 (15.85)		
Total outpatient costs							
Mean (SD)	1,331 (3,928)	63.0	9,776 (10,281)	67.8	5,574 (12,540)	75.1	<.0001
Median (IQR)	588 (1,133)		7061 (7,752)		1990 (3,153)		
Outpatient drug costs							
Mean (SD)	368 (1,697)	17.4	3,964 (7,882)	27.5	3,015 (10,210)	40.6	<.0001
Median (IQR)	56 (243)		1,034 (3,564)		350 (1,253)		
Total ER costs							
Mean (SD)	63 (218)	3.0	119 (396)	0.8	124 (580)	1.7	<.0001
Median (IQR)	0 (44)		0 (94)		0 (80)		
Days of inpatient care							
Mean (SD)	0.09 (0.66)		0.44 (1.13)		0.24 (1.15)		<.0001
Median (IQR)	0.00 (0.00)		0.17 (0.30)		0.00 (0.10)		
Inpatient visits							
Mean (SD)	0.01 (0.05)		0.13 (0.17)		0.24 (1.15)		<.0001
Median (IQR)	0.00 (0.00)		0.16 (0.15)		0.00 (0.10)		
Outpatient visits							
Mean (SD)	1.30 (1.24)		2.70 (1.30)		2.17 (1.47)		<.0001
Median (IQR)	0.98 (1.38)		2.49 (1.50)		1.89 (1.72)		
ER visits							
Mean (SD)	0.02 (1.47)		0.03 (0.08)		0.03 (0.09)		<.0001
Median (IQR)	0.00 (0.02)		0.00 (0.04)		0.00 (0.03)		

BC = breast cancer, BCF = breast cancer free, ER = emergency room, IQR = interquartile range, MBC = metastatic breast cancer, SD = standard deviation.

Table 3

Adjusted healthcare costs of MBC, BC, and BCF patients.

Cost ratios	Total costs	95% CI	OP costs	95% CI	OP drug costs	95% CI	IP costs	95% CI	IP drug costs	95% CI	ER costs	95% CI
Intercept	2,539.79*	1,922.32 | 3,355.58	895.12*	685.88 | 1,168.19	211.27*	141.78 | 314.81	3,990.99*	2,808.20 | 5,671.98	1,041.10*	546.07 | 1,984.87	185.09*	123.79 | 276.76
Group												
BCF	1.00		1.00		1.00		1.00		1.00		1.00	
MBC	4.08*	3.84–4.34	4.72*	4.45–5.00	10.42*	9.56–11.36	1.60*	1.44–1.78	2.31*	1.89–2.83	1.65*	1.50–1.81
BC	8.86*	8.51–9.22	8.94*	8.61–9.28	15.02*	14.19–15.91	1.69*	1.58–1.81	4.43*	3.86–5.08	1.55*	1.46–1.64
Age												
20–30	1.00		1.00		1.00		1.00		1.00		1.00	
31–40	1.13	0.93–1.39	1.10*	0.91–1.33	1.18	0.89–1.56	1.53*	1.19–1.96	1.78*	1.13–2.81	1.34	0.99–1.81
41–50	1.13	0.93–1.38	1.20*	1.00–1.45	1.27	0.96–1.67	1.30*	1.02–1.66	1.38*	0.89–2.15	1.33	0.99–1.78
51–60	1.35*	1.11–1.64	1.48*	1.23–1.78	1.68*	1.28–2.22	1.27	0.99–1.61	1.28*	0.82–1.99	1.44*	1.08–1.93
61–70	1.68*	1.37–2.04	1.79*	1.48–2.16	2.20*	1.66–2.91	1.36*	1.06–1.74	1.12*	0.71–1.77	2.03*	1.51–2.73
71–80	2.08*	1.69–2.57	1.82*	1.49–2.22	2.22*	1.65–2.99	1.86*	1.44–2.41	1.51*	0.94–2.44	2.41*	1.78–3.28
>=81	2.64*	2.04–3.42	1.93*	1.51–2.47	2.13*	1.48–3.07	2.15*	1.58–2.94	1.15*	0.65–2.04	3.49*	2.45–4.96
Residential area												
Northern	1.00		1.00		1.00		1.00		1.00		1.00	
Central	0.42*	0.35–0.52	0.79*	0.65–0.95	0.72*	0.54–0.96	0.46*	0.35–0.59	0.25*	0.15–0.41	0.48*	0.37–0.64
Southern	0.46*	0.38–0.57	0.86	0.71–1.05	0.77	0.58–1.04	0.46*	0.36–0.60	0.21*	0.13–0.35	0.54*	0.41–0.72
Eastern	0.49*	0.40–0.60	0.88	0.73–1.07	0.80	0.60–1.07	0.54*	0.41–0.70	0.29*	0.18–0.48	0.42*	0.31–0.56
CCI score												
CCI=0	1.00		1.00		1.00		1.00		1.00		1.00	
CCI=1	1.92*	1.82	1.87*	1.77–1.97	2.24*	2.07–2.43	1.33*	1.24–1.43	1.50*	1.31–1.72	1.45*	1.34–1.57
CCI≥2	3.07*	2.79	2.24*	2.04–2.45	2.90*	2.53–3.32	2.28*	2.03–2.57	3.42*	2.72–4.30	2.29*	2.01–2.61

BC = breast cancer, BCF = breast cancer free, CCI = Charlson Comorbidity Index, ER=emergency room, IP=inpatient, MBC = metastatic breast cancer, OP=outpatient.
* $P < .05$.

3.3.1. HER2 and endocrine therapy. It was found that patients receiving both HER2-targeted therapy and endocrine therapy had the greatest PPPM total, outpatient, and outpatient drug costs while those under only HER2-targeted therapy had the greatest PPPM total inpatient, inpatient drug, and ER costs (Table 4). In addition, patients receiving both HER2-targeted therapy and endocrine therapy had the greatest number of outpatient visits while those under HER2-targeted therapy had the greatest number of inpatient visits and ER visits.

3.3.2. de novo MBC vs. recurrent MBC. The subgroup analysis results also showed that overall and all various types of costs were significantly higher in the de novo MBC group compared with the recurrent MBC group. Specifically, the adjusted PPPM total

Table 4

Adjusted healthcare costs of HER2 and endocrine therapy subgroups.

Cost ratios	Total costs	95% CI	OP costs	95% CI	OP drug costs	95% CI	IP costs	95% CI	IP drug costs	95% CI	ER costs	95% CI
Intercept	2,403.35*	1,830.62 | 3,155.73	787.04*	608.15 | 1,018.56	173.69*	117.88 | 255.94	3,958.30*	2,787.33 | 5,621.19	999.62*	524.96 | 1,903.46	183.70*	122.95 | 274.49
Group												
BCF	1.00		1.00		1.00		1.00		1.00		1.00	
MBC												
HER2 (+) ER(+)	28.08*	20.99–37.58	38.92*	29.57–51.24	137.81*	91.89–206.69	2.24*	1.58–3.18	6.50*	3.41–12.37	2.18*	1.49–3.18
HER2 (+) ER(−)	21.57*	15.01–31.00	26.58*	18.88–37.44	85.51*	51.63–141.62	3.84*	2.52–5.85	10.05*	4.63–21.80	5.70*	3.55–9.16
HER2 (−) ER(+)	3.90*	3.60–4.22	4.20*	3.89–4.53	6.50*	5.82–7.27	1.67*	1.46–1.90	1.81*	1.41–2.33	1.70*	1.50–1.92
HER2 (−) ER(−)	1.69*	1.55–1.83	1.76*	1.63–1.91	1.94*	1.72–2.18	1.07	0.90–1.25	1.26	0.93–1.71	1.23*	1.08–1.41
BC	8.85*	8.51–9.20	8.94*	8.61–9.27	15.08*	14.26–15.95	1.68*	1.57–1.80	4.38*	3.82–5.02	1.54*	1.45–1.64
Age												
20–30	1.00		1.00		1.00		1.00		1.00		1.00	
31–40	1.10	0.90–1.33	1.07	0.89–1.28	1.11	0.84–1.46	1.52*	1.18–1.94	1.78*	1.13–2.80	1.33	0.99–1.80
41–50	1.11	0.92–1.34	1.19*	0.99–1.42	1.24	0.95–1.62	1.29*	1.01–1.64	1.36	0.88–2.12	1.33*	0.99–1.77
51–60	1.32*	1.09–1.59	1.45*	1.21–1.73	1.65*	1.26–2.16	1.26	0.99–1.60	1.30	0.83–2.02	1.45*	1.08–1.93
61–70	1.65*	1.36–2.01	1.76*	1.46–2.11	2.14*	1.63–2.81	1.36*	1.07–1.74	1.15	0.73–1.81	2.00*	1.49–2.69
71–80	1.99*	1.62–2.44	1.73*	1.42–2.09	2.11*	1.58–2.81	1.83*	1.41–2.37	1.49*	0.93–2.40	2.43*	1.79–3.30
>=81	2.67*	2.08–3.44	1.95*	1.53–2.47	2.20*	1.55–3.14	2.18*	1.60–2.37	1.22	0.69–2.16	3.54*	2.50–5.04
Residential area												
Northern	1.00		1.00		1.00		1.00		1.00		1.00	
Central	0.46*	0.38–0.56	0.92*	0.76–1.10	0.90	0.68–1.19	0.47*	0.36–0.61	0.27*	0.16–0.43	0.49*	0.37–0.65
Southern	0.50*	0.41–0.62	1.01*	0.84–1.22	0.98	0.74–1.30	0.47*	0.36–0.61	0.22*	0.14–0.37	0.55*	0.42–0.74
Eastern	0.53*	0.43–0.65	1.02*	0.85–1.23	0.99	0.75–1.32	0.55*	0.42–0.72	0.31*	0.19–0.51	0.42*	0.32–0.56
CCI score												
CCI=0	1.00		1.00		1.00		1.00		1.00		1.00	
CCI=1	1.91*	1.80–2.02	1.88*	1.78–1.97	2.27*	2.10–2.45	1.30*	1.21–1.40	1.41*	1.23–1.62	1.40*	1.29–1.51
CCI≥2	3.06*	2.78–3.36	2.24*	2.05–2.44	2.90*	2.54–3.30	2.27*	2.01–2.56	3.41*	2.71–4.28	2.27*	2.00–2.59

CCI = Charlson Comorbidity Index, CI=confidence interval, ER=emergency room, HER2 = human epidermal growth factor receptor 2, IP=inpatient, MBC = metastatic breast cancer, OP=outpatient.
* $P < .05$.

Table 5

Adjusted healthcare costs of de novo MBC and recurrent MBC patients.

Cost ratios	Total costs	95% CI	OP costs	95% CI	OP drug costs	95% CI	IP costs	95% CI	IP drug costs	95% CI	ER costs	95% CI
Intercept	2,495.53*	1,898.79 | 3,279.82	789.46*	608.54 | 1,024.18	174.12*	117.48 | 258.07	4,056*	2,855.39 | 5,761.44	1,027.02*	541.73 | 1,968.25	220.7*	147.86 | 329.43
Group												
BCF	1.00		1.00		1.00		1.00		1.00		1.00	
MBC												
Recurrent MBC	2.31*	2.16–2.46	2.62*	2.46–2.78	4.68*	4.27–5.14	1.24*	1.09–1.41	1.81*	1.42–2.31	1.14*	1.03–1.27
De novo MBC	12.16*	10.71–13.82	14.29*	12.65–16.13	36.31*	30.32–43.49	2.15*	1.85–2.51	3.04*	2.29–4.03	3.39*	2.84–4.05
BC	8.82*	8.48–9.17	8.89*	8.56–9.22	14.85*	14.03–15.71	1.69*	1.58–1.81	4.41*	3.85–5.06	1.54*	1.46–1.64
Age												
20–30	1.00		1.00		1.00		1.00		1.00		1.00	
31–40	1.11	0.91–1.35	1.09	0.91–1.32	1.21	0.91–1.59	1.51*	1.18–1.94	1.78*	1.13–2.80	1.29	0.96–1.73
41–50	1.10	0.91–1.33	1.17	0.98–1.41	1.23	0.94–1.62	1.29*	1.01–1.64	1.38	0.89–2.16	1.31	0.98–1.74
51–60	1.29*	1.06–1.56	1.42*	1.19–1.71	1.61*	1.22–2.11	1.25*	0.98–1.59	1.28	0.82–1.99	1.40*	1.05–1.87
61–70	1.61*	1.32–1.95	1.71*	1.43–2.06	2.07*	1.57–2.73	1.35*	1.06–1.73	1.13	0.72–1.77	1.94*	1.44–2.60
71–80	1.93*	1.57–2.37	1.67*	1.37–2.03	2.00*	1.47–2.64	1.82*	1.41–2.36	1.49	0.93–2.40	2.36*	1.74–3.20
>=81	2.54*	1.97–3.27	1.87*	1.47–2.38	2.05*	1.43–2.93	2.13*	1.56–2.90	1.15	0.64–2.04	3.46*	2.44–4.91
Residential area												
Northern	1.00		1.00		1.00		1.00		1.00		1.00	
Central	0.45*	0.37–0.55	0.93	0.77–1.12	0.92	0.70–1.23	0.45*	0.35–0.59	0.25*	0.16–0.41	0.42*	0.32–0.55
Southern	0.49*	0.40–0.60	1.00	0.83–1.22	0.96	0.72–1.29	0.46*	0.35–0.60	0.22*	0.13–0.36	0.47*	0.35–0.62
Eastern	0.52*	0.42–0.63	1.04	0.86–1.25	1.02	0.76–1.35	0.53*	0.41–0.69	0.30*	0.18–0.48	0.36*	0.27–0.48
CCI score												
CCI=0	1.00		1.00		1.00		1.00		1.00		1.00	
CCI=1	1.94*	1.83–2.05	1.87*	1.78–1.98	2.25*	2.08–2.44	1.34*	1.24–1.44	1.50*	1.31–1.72	1.45*	1.34–1.57
CCI≥2	3.03*	2.76–3.33	2.20*	2.01–2.40	2.83*	2.48–3.24	2.29*	2.03–2.58	3.40*	2.70–4.28	2.28*	2.00–2.59

CCI = Charlson Comorbidity Index, ER=emergency room, IP=inpatient, MBC = metastatic breast cancer, OP=outpatient.
* $P < .05$.

healthcare cost ratio of recurrent MBC to BCF was 2.31, compared to 12.16 in the de novo group (Table 5). In addition, de novo MBC patients were more likely than BCF patients to have outpatient, inpatient, and ER visits with adjusted ratios of 2.10, 8.75, and 2.63, respectively; the corresponding ratios in the recurrent group were 1.57, 1.85, and 1.15 visits.

3.3.3. Progression vs. progression-free. Moreover, in the comparison between progression and progression-free MBC patients, the adjusted PPPM overall and all various types of costs were significantly higher in the progression group than in those progression-free patients. The ratio of monthly healthcare total costs of MBC patients with progression to that of BCF patients was 16.28 compared to 2.71 in the progression-free group (Table 6). Consistently, the outpatient visits, inpatient visits, and ER visits were all higher in the progression group than in the progression-free group.

4. Discussion

Using a national health insurance claims database, we examined healthcare utilization and costs among patients with MBC. This

Table 6

Adjusted healthcare costs of MBC progression and MBC progression free patients.

Cost ratios	Total costs	95% CI	OP costs	95% CI	OP drug costs	95% CI	IP costs	95% CI	IP drug costs	95% CI	ER costs	95% CI
Intercept	2,479	1,885.40 | 3,261.91	808.11	623.09 | 1048.06	179.72*	121.58 | 265.68	3,988.32*	2,806.56 | 5,667.68	1,027.02	539.15 | 1,956.33	193.74*	129.60 | 289.62
Group												
BCF	1.00		1.00		1.00		1.00		1.00		1.00	
MBC												
Progression	16.28*	13.76–19.28	21.12*	18.00–24.77	65.35*	51.6–82.70	1.94*	1.58–2.37	5.03*	3.46–7.31	2.64*	2.13–3.27
Progression free	2.71*	2.54–2.88	2.88*	2.72–3.06	4.31*	3.95–4.71	1.51*	1.34–1.70	1.61*	1.30–2.00	1.47*	1.33–1.62
BC	8.87*	8.53–9.22	8.95*	8.63–9.29	15.13*	14.3–16.01	1.69*	1.58–1.81	4.47*	3.90–5.13	1.55*	1.46–1.64
Age												
20–30	1.00		1.00		1.00		1.00		1.00		1.00	
31–40	1.10	0.90–1.34	1.07	0.89–1.29	1.12	0.85–1.48	1.53*	1.19–1.95	1.77*	1.12–2.79	1.31	0.98–1.77
41–50	1.11	0.91–1.34	1.18	0.98–1.41	1.21	0.93–1.59	1.30*	1.02–1.65	1.37	0.88–2.13	1.32	0.98–1.76
51–60	1.31*	1.08–1.59	1.43*	1.19–1.72	1.59*	1.21–2.09	1.26*	0.99–1.61	1.27	0.82–1.98	1.44*	1.07–1.92
61–70	1.62*	1.33–1.97	1.71*	1.42–2.06	2.04*	1.55–2.69	1.36*	1.06–1.73	1.14	0.72–1.79	2.03*	1.51–2.72
71–80	1.99*	1.62–2.45	1.71*	1.41–2.08	2.07*	1.55–2.76	1.86*	1.44–2.41	1.55	0.96–2.49	2.39*	1.76–3.25
>=81	2.59*	2.01–3.34	1.87*	1.47–2.37	2.03*	1.42–2.90	2.16*	1.58–2.94	1.18	0.67–2.10	3.48*	2.45–4.95
Residential area												
Northern	1.00		1.00		1.00		1.00		1.00		1.00	
Central	0.44*	0.36–0.54	0.90	0.74–1.08	0.88	0.67–1.17	0.46*	0.35–0.59	0.25*	0.16–0.41	0.47*	0.35–0.62
Southern	0.49*	0.40–0.60	0.99	0.82–1.19	0.96	0.72–1.27	0.47*	0.36–0.61	0.22*	0.13–0.35	0.52*	0.39–0.69
Eastern	0.51*	0.42–0.63	1.00	0.83–1.21	0.97	0.73–1.30	0.54*	0.41–0.70	0.29*	0.18–0.48	0.40*	0.30–0.54
CCI score												
CCI=0	1.00		1.00		1.00		1.00		1.00		1.00	
CCI=1	1.97*	1.86–2.08	1.93*	1.83–2.04	2.39*	2.21–2.59	1.33*	1.24–1.43	1.51*	1.32–1.73	1.45*	1.34–1.57
CCI≥2	3.09*	2.81–3.39	2.29*	2.09–2.50	2.99*	2.62–3.41	2.28*	2.02–2.57	3.43*	2.73–4.30	2.29*	2.01–2.60

CCI = Charlson Comorbidity Index, ER=emergency room, IP=inpatient, MBC = metastatic breast cancer, OP=outpatient.
* $P < .05$.

retrospective population-based national study has several strengths. First, our data sources were a nationwide cancer registry and claims database, which made our study sample representative of the population in Taiwan and enhanced the external validity of our study findings. Second, the relatively large sample size provided us with great statistical power. Third, in addition to comparison among BCF, BC, and MBC patients, subgroup analyses were also conducted. Lastly, it is the first study in Taiwan, and 1 of the few of its kind in Asia, to utilize the NHCD and TCDB to investigate MBC healthcare costs and utilization.

In our study, considerably more MBC patients received endocrine therapy than HER-2 targeted therapy (51.2% vs 5.4%), which is similar to what has been reported in other epidemiological studies of MBC in Taiwan and in the US.[15,16] The infrequent use of HER2 targeted therapy observed is likely due to the restriction of use and limited coverage provided by the National Health Insurance. In Taiwan, the NHI allows the use of trastuzumab in MBC patients only if they have not been treated with trastuzumab at an earlier stage of BC, have been treated only with chemotherapy one time at a metastatic stage of BC, or if it is combined with paclitaxel or docetaxel with no history of prior chemotherapy. As such, if study patients did not meet those requirements, they may have paid out-of-pocket, and those treatment records would not be captured by our study database.

A cost analysis of MBC in the U.S. conducted by Meyer et al[6] revealed that the PPPM for all-cause healthcare expenditure among patients receiving HER2-targeted therapy was $14,105, or $2,649 higher than among patients without that therapy. A recent U.S. evaluation of health costs of HER2-positive BC reported that the PPPM healthcare cost among MBC patients was $13,000 to $34,000 higher than those without MBC.[17] Moreover, HER2-targeted therapy drug costs were found to be 1 of the primary cost contributors. Similarly, our subgroup analysis found that receiving HER2 targeted therapy had higher cost ratios than the other treatment groups. All HER2-targeted drugs are very costly; for example, trastuzumab is TWD 57,963 per vial in the NHI program in 2018. As such, it is important for policy makers to perform health technology assessments and budget impact analyses on HER2-targeted drugs for drug listing and/or extending benefits. Moreover, a recent estimation of MBC burden in Spain showed that total medical cost per MBC patient over 5 years was €290,029 for the HER2+/HR+ group, €248,885 for the HER2+/HR- group, €204,376 for the HER2-/HR+ group, and €94,409 for the triple negative group. Similar trends were observed in our study.[18]

Limited research has been conducted to compare clinical outcomes and healthcare utilization between patients with recurrence and those with de novo MBC. Several exceptions are noteworthy. Engle-Nitz et al estimated the total overall healthcare expenditures of women with HER2 negative and hormone positive MBC.[19] The total expenditure was estimated at $13,414 PPPM in patients with recurrent MBC and at $9,994 PPPM among those with de novo MBC. In contrast, Meyer et al[6] found that MBC patients in the de novo cohort had significantly higher all-cause healthcare costs than the recurrent cohort ($15,223 vs $13,446). The Meyer's study finding is consistent with our subgroup analysis results.

To our surprise, total healthcare costs and most sub-categories of costs for BC were higher than those for MBC. There are a few possible explanations for this finding. First, in several validation studies that used ICD-9-CM codes in the Medicare claims database to identify patients with distant metastatic BC, the sensitivity, specificity, and positive predictive value of the selection did not simultaneously exceed 70%.[20–23] Similarly, the method we used to identify recurrent MBC patients was to use ICD-9 CM diagnosis codes in the NHCD, where potential undercoding or miscoding of metastases may have led to some MBC patients being misclassified into the BC group. Second, owing to the lack of out-of-pocket expenditure data, certain anti-cancer drugs were not included in our analysis. In 2018, 4 targeted therapies have been approved by the Taiwan Food and Drug Administration for patients with HER2-positive MBC, namely, trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine, but only trastuzumab and lapatinib have been reimbursed by the NHI program, and only since 2014. As such, patients' out-of-pocket expenditures for anti-cancer drug treatments were not captured by the study claim database and may have led to an underestimation of the total medical costs of MBC patients. Lastly, the NHI's restriction of trastuzumab use in MBC patients and the relatively high costs of HER2-targeted therapy, the standard care for HER-2 positive early BC, may have also contributed to the differences in costs between BC and MBC groups.[24–26]

This study has a few limitations. First, due to database limitations, information about patients' disease severity and socioeconomic background was not available and was therefore not taken into account in the analysis. Second, using ICD-9 codes to identify patients with recurrent MBC may have resulted in misclassification and may have conflicted with clinical/ pathological diagnoses. As a result, the healthcare costs and/or utilization of the MBC group may have been underestimated. Third, our follow-up period was relatively short, with a maximum length of 4 years. A few newer anti-cancer drugs' effects on the outcomes of interest may not have been fully captured (e.g., lapatinib and eribulin, which began to be reimbursed by the NHI program in 2014). Fourth, due to the lack of info about drug use history before MBC diagnosis, we may have failed to identify all patients who had received HER2-targeted therapy or endocrine therapy.

MBC poses a significant financial burden on the NHI program and on society. The introduction of more effective but costly HER-2 targeted therapies or other target therapies in the treatment of MBC has contributed to the rise of healthcare resource use for MBC patients. From the NHI perspective, understanding how healthcare utilization and payments vary between MBC and BC patients may guide decisions about medical benefits when facing healthcare resource constraints. From the patient's perspective, the findings could provide a better understanding of the total medical costs of MBC. From a researcher's perspective, this study provides cost estimates for subgroups of patients by disease type, by presence of progression, and by phenotype/treatment type. The findings also provide essential data for future pharmacoeconomic studies, such as cost-effectiveness analyses and cost-utility analyses.

5. Conclusion

This study demonstrated that MBC is associated with substantial healthcare costs in Taiwan. Among MBC and BC patients, both healthcare costs and utilization were mostly due to outpatient visits, followed by inpatient visits and ER visits. It was found that patients with de novo or progressed MBC as well as those receiving HER-2 targeted therapy had significantly higher

healthcare costs and utilization. The study findings provide essential data for MBC and BC-related economic evaluations that may aid in health expenditure allocation.

Author contributions

Conceptualization: Hsuan-Ming Chen, Shao-Chin Chiang, Yu Ko.
Formal analysis: Hsuan-Ming Chen, Yi-Chun Lin.
Funding acquisition: Yu Ko.
Investigation: Shao-Chin Chiang, Yu Ko.
Methodology: Hsuan-Ming Chen, Jin-Hua Chen, Yi-Chun Lin, Yu Ko.
Supervision: Yu Ko.
Validation: Jin-Hua Chen.
Writing – original draft: Hsuan-Ming Chen.
Writing – review & editing: Jin-Hua Chen, Shao-Chin Chiang, Yi-Chun Lin, Yu Ko.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–386.
[2] Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review 1975-2015. Bethesda, Maryland: National Cancer Institute; 2018.
[3] Liu FC, Lin HT, Kuo CF, See LC, Chiou MJ, Yu HP. Epidemiology and survival outcome of breast cancer in a nationwide study. Oncotarget 2017;8:16939–50.
[4] Health Promotion Administration, Ministry of Health, Welfare, Cancer Registry annual report 2018 Taiwan. Taipei: Health Promotion Administration, Ministry of Health and Welfare; 2020.
[5] Montero AJ, Eapen S, Gorin B, Adler P. The economic burden of metastatic breast cancer: a U.S. managed care perspective. Breast Cancer Res Treat 2012;134:815–22.
[6] Meyer N, Hao Y, Song X, et al. Healthcare resource use and expenditures among metastatic breast cancer patients treated with HER2-targeted agents. Int J Breast Cancer 2014;2014:475171.
[7] Lage MJ, Borker R, Barber B, Gao S. Healthcare costs in postmenopausal women with hormone-positive metastatic breast cancer. J Med Econ 2010;13:691–7.
[8] Burton T, Byfield SD, Smith GL, et al. Clinical and economic outcomes by first-line treatment among women with HR+/HER2- metastatic breast cancer in a large US health plan database. Curr Med Res Opin 2016;32:1417–23.
[9] National Health Insurance Administration, Ministry of Health, Welfare, Statistics on the top 10 medical expenditure by type of cancer in health insurance. Taipei: National Health Insurance Administration, Ministry of Health and Welfare; 2020.
[10] Ray S, Bonthapally V, McMorrow D, Bonafede M, Landsman-Blumberg P. Patterns of treatment, healthcare utilization and costs by lines of therapy in metastatic breast cancer in a large insured US population. J Comp Eff Res 2013;2:195–206.
[11] Vera-Llonch M, Weycker D, Glass A, et al. Healthcare costs in women with metastatic breast cancer receiving chemotherapy as their principal treatment modality. BMC Cancer 2011;11:250.
[12] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–9.
[13] Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ.* 1980: 23–32.
[14] Joshi V, Adelstein BA, Schaffer A, Srasuebkul P, Dobbins T, Pearson SA. Validating a proxy for disease progression in metastatic cancer patients using prescribing and dispensing data. Asia Pac J Clin Oncol 2017;13:e246–52.
[15] American Cancer Society. Breast Cancer Facts & Figures 2017-2018. Atlanta: American Cancer Society; 2019.
[16] Health Promotion Administration, Ministry of Health, Welfare,Site-Specific Factors Distribution Statistics. Taipei: Health Promotion Administration, Ministry of Health and Welfare; 2015.
[17] Sussell JA, Sheinson D, Wu N, Shah-Manek B, Seetasith A. HER2-positive metastatic breast cancer: a retrospective cohort study of healthcare costs in the targeted-therapy age. Adv Ther 2020;37:1632–45.
[18] Bermejo de Las Heras B, Cortes Ramon YCJ, Galve Calvo E, et al. The economic burden of metastatic breast cancer in Spain. Eur J Hosp Pharm 2020;27:19–24.
[19] Engel-Nitz NM, Hao Y, Becker LK, Gerdes R. Costs and mortality of recurrent versus de novo hormone receptor-positive/HER2(−) metastatic breast cancer. J Comp Eff Res 2015;4:303–14.
[20] Chawla N, Yabroff KR, Mariotto A, McNeel TS, Schrag D, Warren JL. Limited validity of diagnosis codes in Medicare claims for identifying cancer metastases and inferring stage. Ann Epidemiol 2014;24:666–72. 672 e661-662.
[21] Nordstrom BL, Whyte JL, Stolar M, Mercaldi C, Kallich JD. Identification of metastatic cancer in claims data. Pharmacoepidemiol Drug Saf 2012;21(Suppl 2):21–8.
[22] Warren JL, Yabroff KR. Challenges and opportunities in measuring cancer recurrence in the United States. J Natl Cancer Inst 2015;107:1–8.
[23] Whyte JL, Engel-Nitz NM, Teitelbaum A, Gomez Rey G, Kallich JD. An evaluation of algorithms for identifying metastatic breast, lung, or colorectal cancer in administrative claims data. Med Care 2015;53:e49–57.
[24] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164–72.
[25] Esserman LJ, Berry DA, DeMichele A, et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL–CALGB 150007/150012, ACRIN 6657. J Clin Oncol 2012;30:3242–9.
[26] Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372:134–41.