



# Direct medical cost of adjuvant systemic treatment for HER2-positive breast cancer in Vietnam

[Costo médico directo del tratamiento sistémico adyuvante para el cáncer de mama HER2 positivo en Vietnam]

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## Abstract

**Context:** HER2-positive breast cancer, one of the most aggressive subtypes of breast cancer, is associated with the high cost of HER2-targeted therapies. However, its financial burden in Vietnam has not been fully investigated.

**Aims:** To determine the direct medical costs associated with HER2-positive breast cancer treatment in Vietnam from the perspective of healthcare payers, including social health insurance providers and patients.

**Methods:** A multicenter study was conducted in two tertiary hospitals from January to December 2022. Retrospective patient-level data of 303 HER2-positive breast cancer patients who underwent adjuvant systemic treatment for initial treatment was analyzed. A micro-costing bottom-up approach was used to estimate the direct medical cost per inpatient admission in 2022. All cost calculations are presented as USD values using an exchange rate in 2022.

**Results:** The average cost per inpatient admission was \$680.0 ± \$431.7. Of these, out-of-pocket costs accounted for approximately 42%. Drug costs were the main driver of total spending (92.9%), followed by hospital beds (2.2%), laboratory tests, and diagnostic imaging (2%). The cost of HER2-targeted therapy was responsible for 82.9% of the total direct medical cost. The average cost per inpatient admission of patients receiving chemotherapy with anti-HER2 agents was seven times higher than that of patients receiving chemotherapy alone (\$864.0 vs. \$120.6). Factors affecting the cost per inpatient admission were age, residence (urban or rural), occupation, and health insurance reimbursement rate.

**Conclusions:** HER-positive breast cancer treatment imposes a significant financial burden in Vietnam, particularly with regimens containing HER2-targeted therapies. The findings of our study add to the increasing literature on the cost of breast cancer treatment and can contribute to the pharmaco-economic analysis of HER2-positive breast cancer treatment in Vietnam.

**Keywords:** adjuvant; breast cancer; cost; HER2-positive; systemic treatment; Vietnam.

## Resumen

**Contexto:** El cáncer de mama HER2-positivo, uno de los subtipos más agresivos de cáncer de mama, está asociado con el alto costo de las terapias dirigidas a HER2. Sin embargo, su carga financiera en Vietnam no se ha investigado por completo.

**Objetivos:** Determinar los costos médicos directos asociados con el tratamiento del cáncer de mama HER2-positivo en Vietnam desde la perspectiva de los pagadores de atención médica, incluidos los proveedores de seguros sociales de salud y los pacientes.

**Métodos:** Se realizó un estudio multicéntrico en dos hospitales terciarios de enero a diciembre de 2022. Se analizaron datos retrospectivos a nivel de paciente de 303 pacientes con cáncer de mama HER2-positivo que se sometieron a un tratamiento sistémico adyuvante para el tratamiento inicial. Se utilizó un enfoque de micro-costeo ascendente para estimar el costo médico directo por ingreso hospitalario en 2022. Todos los cálculos de costos se presentan como valores en dólares estadounidenses utilizando un tipo de cambio en 2022.

**Resultados:** El costo promedio por ingreso hospitalario fue de \$680,0 ± \$431,7. De estos, los costos de bolsillo representaron aproximadamente el 42%. Los costos de los medicamentos fueron el principal impulsor del gasto total (92,9%), seguido de las camas de hospital (2,2%), las pruebas de laboratorio y las imágenes diagnósticas (2%). El costo de la terapia dirigida a HER2 fue responsable del 82,9% del costo médico directo total. El costo promedio por admisión hospitalaria de pacientes que recibieron quimioterapia con agentes anti-HER2 fue siete veces mayor que el de los pacientes que recibieron quimioterapia sola (\$864,0 frente a \$120,6). Los factores que afectaron el costo por admisión hospitalaria fueron la edad, la residencia (urbana o rural), la ocupación y la tasa de reembolso del seguro médico.

**Conclusiones:** El tratamiento del cáncer de mama HER-positivo impone una carga financiera significativa en Vietnam, en particular con regímenes que contienen terapias dirigidas a HER2. Los hallazgos de nuestro estudio se suman a la creciente literatura sobre el costo del tratamiento del cáncer de mama y pueden contribuir al análisis farmacoeconómico del tratamiento del cáncer de mama HER2-positivo en Vietnam.

**Palabras Clave:** adyuvante; cáncer de mama; costo; HER2-positivo; tratamiento sistémico; Vietnam.

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## INTRODUCTION

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Breast cancer is the most common type of cancer and the leading cause of cancer deaths among women worldwide. Its occurrence is evident from an estimated 2.3 million new cases and 666,103 deaths being globally reported in 2022 (World Health Organization, 2024). In Vietnam, breast cancer is recognized as the most prevalent cancer among women and in both sexes, with over 24,500 newly diagnosed cases. Moreover, it ranks fourth among the leading causes of cancer-related deaths in Vietnamese women, claiming the lives of over 10,000 individuals in 2022 (World Health Organization, 2024).

Recent advances in molecular biology have revealed that breast cancer is a highly heterogeneous disease that can be classified into several subtypes with diverse clinical characteristics and varying prognoses. Of which, about 15-20% of breast cancers with overexpression of human epidermal growth factor receptor 2 (HER2) are defined as HER2-positive breast cancers and are one of the most aggressive phenotypes with poor prognosis (Furrer et al., 2018; Gonzalez-Angulo et al., 2009; Loibl and Gianni, 2017; Slamon et al., 1987).

The discovery of revolutionary anti-HER2 therapies (e.g., trastuzumab, pertuzumab) has changed the course of treatment and improved the prognosis of HER2-positive breast cancer patients. These agents have led to higher rates of progression-free survival, overall survival, and overall response rate compared to chemotherapy alone (Loibl and Gianni, 2017; Swain et al., 2023; Wang and Xu, 2019).

Adjuvant treatment is given after surgery for breast cancer. It may be separated into local treatment (radiotherapy) and systemic treatments (chemotherapy, endocrine, and targeted therapies) (Flatley and Dodwell, 2019). For systemic treatment courses, patients must be admitted to the hospital every chemotherapy cycle for initial treatment. According to the guidelines of many countries, including Vietnam, the 1-year administration of trastuzumab (plus pertuzumab or not) with chemotherapy regimens is currently recommended as standard treatment for HER2-positive early-stage breast cancer in adjuvant settings. However, anti-HER2 agents associated with high costs may have led to rising costs of HER2-positive breast cancer treatment. Studies in Portugal and Japan have shown that the average cost of treatment for HER2-positive breast cancer was higher than that of patients with HER2-negative and triple-negative breast cancer, mainly driven by the cost of HER2-targeted therapy (Brandão et al., 2020; Nishikawa et al., 2024).

Several studies have assessed the treatment costs of breast cancer in Vietnam by evaluating the direct medical and out-of-pocket costs for the general population of Vietnamese patients with breast cancer (Hoang Lan et al., 2013; Jenkins et al., 2018; Ngan et al., 2022). However, to the best of our knowledge, studies on the cost of HER2-positive breast cancer subtypes in the early stages are limited (Brandão et al., 2020; Nishikawa et al., 2024; Spanggaard et al., 2022), and no study to date has focused on the economic burden of treatment for HER2-positive breast cancer subtypes in Vietnam. This study aimed to estimate the direct medical cost of adjuvant systemic treatment for HER2-positive breast and its associated factors. The findings of our study contribute to the developing literature on the cost of breast cancer treatment and can support the pharmacoeconomic analysis of HER2-targeted therapies in Vietnam.

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## MATERIAL AND METHODS

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### Study design

This study was conducted at two tertiary hospitals in northern and central Vietnam. The direct medical costs per inpatient admission of adjuvant systemic treatment were analyzed from the perspective of healthcare payers, including the costs incurred by patients and social health insurance. Using a micro-costing bottom-up approach, we estimated the cost from patient-level data via inpatient medical records and medical bills for 1 year from January to December 2022.

### Ethics statement

This study was approved by the Ethics Committee of the Hue University of Medicine and Pharmacy, Vietnam (Code: H2022/495, dated September 20, 2022) and was performed in agreement with the Board of Directors of the two tertiary hospitals involved.

### Study population

By using medical records, patients presenting with HER2-positive early-stage breast cancer were selected according to the following criteria: (1) diagnosis of primary breast cancer identified by the C50 diagnostic code (based on the International Statistical Classification of Diseases and Related Health Problems-ICD-10), (2) female patients aged 18 and above, (3) diagnosed with HER2-positive breast cancer based on immunohistochemistry (IHC) test score of 3+ or an IHC result of 2+ along with a positive fluorescence in situ hybridization test result, (4) received systemic

therapy for adjuvant treatment during the first year following diagnosis (including chemotherapy only, chemotherapy in combination with HER2-targeted therapy, or HER2-targeted therapy with/without hormone therapy), and (5) received at least three cycles of systematic treatment from January 1, 2022, to December 31, 2022. Patients were excluded if they were pregnant during systemic treatment or were simultaneously diagnosed with other types of cancer in 2022. Based on the inclusion and exclusion criteria, all eligible patients from the two hospitals during the study period were included.

### Data collection

The collected data were classified into three major categories: patient characteristics, treatment regimens, and cost of inpatient treatment. We collected data on patient characteristics and treatment processes from medical records. The data included age, residence, occupation, social health insurance reimbursement rate, cancer stage at diagnosis, comorbidities, hormone receptor status, and treatment regimens.

Direct medical costs were identified to assess the economic burden of adjuvant systemic treatment for HER2-positive breast cancer from a healthcare payer's perspective, encompassing expenses related to hospital beds, laboratory tests, diagnostic imaging, drugs, and other medical costs, such as procedures and supplies. These costs were meticulously analyzed by categorizing them into specific dimensions and indicators. Hospital bed costs were calculated based on the duration of stay and daily bed rates, with the total cost calculated by multiplying the number of days of stay by the daily bed cost. Laboratory test costs were derived by identifying test types, frequencies, and associated costs, with the total cost derived from summing the costs of all tests performed during each inpatient admission. Diagnostic imaging costs were assessed by evaluating imaging procedures' type, frequency, and cost, and the total cost accumulated from all diagnostic imaging activities. Drug costs were calculated by considering administered drugs' types, dosages, and frequencies. Other medical costs were detailed by examining the types and frequencies of procedures and the associated medical supplies. Direct non-medical costs (e.g., travel, accommodation, and meals) and indirect costs (e.g., lost income or premature death due to the disease) were not included in these analyses. Moreover, cost data were collected via medical bills for adjuvant systemic treatment; therefore, the costs of comorbidity treatment were not estimated.

### Cost and statistical analysis

Based on the cost reimbursed in the medical bills of inpatient admission, we calculated the average cost per inpatient admission of a patient. The cost per inpatient admission was calculated by dividing the total cost of all inpatient admissions by the number of admissions for each patient in 2022. For the reason that the patients could receive chemotherapy regimens or chemotherapy combined with HER2-targeted therapy regimens, we also analyzed the differences in direct medical costs between the two groups.

As systemic treatments are given in different repeating cycles, we also estimated the cost according to three types of treatment cycles, including chemotherapy alone, chemotherapy with HER2-targeted therapy, and HER2-targeted therapy with/without hormone therapy.

We performed descriptive statistics, including the calculation of means, standard deviations (SD), medians, interquartile ranges (IQR) (25-75<sup>th</sup> percentile), and frequencies, as appropriate for patient demographics and cost categories. Due to the non-normally distributed cost data (the Kolmogorov-Smirnov test, p-values <0.001), the Mann-Whitney test was employed to compare costs between two groups of residence, and hormone receptor status, while the Kruskal-Wallis test was used to compare costs among more than two groups of age, occupation, health insurance reimbursement rate and stage of cancer. The threshold for statistical significance was established at a p-value of less than 0.05. The statistical analyses were performed using Statistical Package for the Social Sciences version 26.0.

All cost calculations are presented as USD 2022 values using an exchange rate between the USD and Vietnamese Dong (VND Dong) of 1.0 USD = 23,681 VND Dong in December 2022. (Regulation No. 6209/TB-KBNN of the Vietnam Ministry of Finance). No discount was applied as the study was limited to a single year.

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## RESULTS

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The study included 303 eligible patients, with 2,861 inpatient admissions in 2022. Table 1 provides a summary of the patient demographics and clinical characteristics. The mean age (SD) of patients at the time of diagnosis was 50.5 (9.7) years, with the most frequent age group being from 50 to 59 years (37.0% of all patients). The study population was evenly divided into rural (55.1%) and urban (44.9%) residences. The most common occupations were employment and business (32.3%), followed by agriculture (30.4%). All patients in this study had social health insurance, and approximately three-fourths of them had a reim-

bursement rate of 80%. At the time of primary diagnosis, most patients were diagnosed with stage II breast cancer (59.7%). Most of the patients did not have any comorbidities (73.6%), and over 50% of the patients exhibited expression of estrogen receptor

(ER) and/or progesterone receptor (PR) (ER- or PR-positive) called hormone-positive. Regarding the systemic regimens, nearly a quarter (24.8%) of eligible patients did not use HER2-targeted therapy in their treatment regimens.

**Table 1.** Characteristics and treatment regimens of patients (N = 303, [%]).

Characteristics	N	%
<b>Age</b>		
<40	43	14.2
40-49	93	30.7
50-59	112	37.0
≥60	55	18.1
<b>Mean ± SD</b>	<b>50.5 ± 9.7</b>	
<b>Residence</b>		
Urban	136	44.9
Rural	167	55.1
<b>Occupation</b>		
Employment/Business	98	32.3
Agriculture	92	30.4
Freelancers/Housework	67	22.1
Retired	46	15.2
<b>Social health insurance reimbursement rates<sup>a</sup></b>		
80%	219	72.3
95%	51	16.8
100%	33	10.9
<b>Stage of cancer</b>		
I	78	25.7
II	181	59.7
III	44	14.6
<b>Comorbidity</b>		
Yes	80	26.4
No	223	73.6
<b>Hormone receptor</b>		
Positive	163	53.8
Negative	140	46.2
<b>Adjuvant systemic regimens</b>		
Chemotherapy only	75 <sup>b</sup>	24.8
Chemotherapy with Her2-targeted therapy	228	75.2

SD: Standard deviation; data are presented as numbers (percentages); <sup>a</sup>: These numbers represent the percentage of the total cost paid by governmental health insurance programs; the remaining percentage is co-paid by patients. <sup>b</sup>: All patients were eligible to use HER2-targeted therapy

**Table 2.** Direct medical cost per inpatient admission (N = 303, 2022 USD).

Cost category	Health insurance payment	Patient payment	Total
<b>Chemotherapy regimens</b>			
Mean ± SD	97.1 ± 61.7	23.5 ± 17.2	120.6 ± 73.8
(%)	(80.5)	(19.5)	(100.0)
Median (IQR)	77.9 (65.1-101.2)	19.5 (16.0-26.4)	98.0 (85.0-119.9)
<b>Chemotherapy with HER2-targeted therapy regimens</b>			
Mean ± SD	491.7 ± 213.1	372.3 ± 151.1	864.0 ± 329.8
(%)	(56.9)	(43.1)	(100.0)
Median (IQR)	460.1 (340.1-602.4)	372.2 (270.5-464.1)	861.2 (611.6-1088.8)
<b>All</b>			
Mean ± SD (%)	394.0 ± 253.3 (57.9)	285.9 ± 199.9 (42.1)	680.0 ± 431.7 (100.0)
Median (IQR)	378.5 (180.2-555.0)	299.3 (86.4-431.5)	703.4 (285.4-1009.0)

SD: standard deviation; IQR: interquartile range, US\$1 = VND23,681 (Source: Vietnamese Ministry of Finance: Exchange rate for foreign currencies in December 2022).

**Table 3.** Direct medical cost per cycle of chemotherapy/trastuzumab.

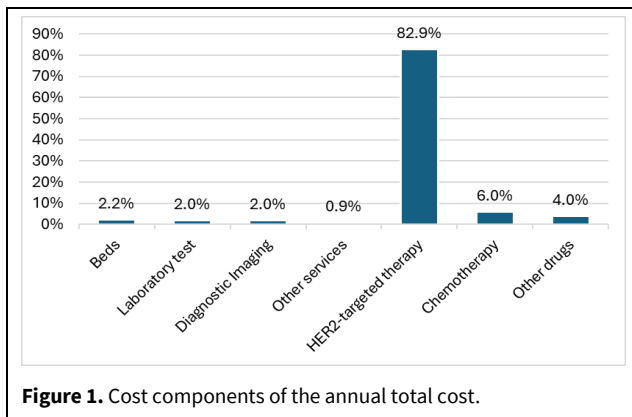
Variable	All	Chemotherapy	Chemotherapy with HER2-targeted therapy	HER2-targeted therapy with/without hormone therapy
(Cost category)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)
Drugs	631.4 ± 424.4	98.0 ± 51.7	1159.1 ± 224.2	1017.5 ± 170.2
Hospital beds	15.1 ± 9.8	13.9 ± 7.0	16.7 ± 8.3	12.3 ± 6.0
Laboratory test	13.7 ± 6.5	17.7 ± 8.2	13.7 ± 8.6	8.9 ± 2.8
Diagnostic Imaging	13.4 ± 22.0	14.6 ± 26.7	9.1 ± 13.0	15.1 ± 28.9
Other medical services	6.4 ± 0.9	6.4 ± 2.4	5.6 ± 0.8	5.7 ± 4.8
<b>All</b>	<b>680.0 ± 431.7</b>	<b>150.7 ± 73.3</b>	<b>1205.6 ± 234.9</b>	<b>1059 ± 184.9</b>

SD: standard deviation; IQR: interquartile range, US\$1 = VND23,681 (Source: Vietnamese Ministry of Finance: Exchange rate for foreign currencies in December 2022).

As shown in Table 2, each patient with HER2-positive breast cancer had an estimated mean cost of \$680 per inpatient admission, of which the insurance covered \$394 (58%), and the patient paid \$285 (42%). Patients receiving chemotherapy regimens with HER2-targeted therapy incurred an average of \$864 per inpatient admission, which was seven times higher than that of patients with chemotherapy alone (\$120). Most of the cost of chemotherapy regimens was covered by social health insurance (80.5%), whereas the insurance reimbursement percentage was only 57% for the cost of chemotherapy regimens with HER2-targeted therapy. On average, patients bore \$372 per admission with HER2-targeted therapy,

which was fifteen times higher than that of chemotherapy regimens (\$23.5).

The costs per treatment cycle are listed in Table 3. Among the types of treatment cycles, the cost per cycle of the combination of chemotherapy and HER2-targeted therapy was the most expensive, with an average of \$1205, followed by the cost of HER2-targeted therapy with/without hormone therapy (\$1059). The difference between the costs of the treatment cycles was owing to the difference in the drug cost per cycle, whereas the other component costs, which accounted for only a small proportion of the total cost, were quite similar.



**Figure 1.** Cost components of the annual total cost.

Fig. 1 illustrates the costs of the different components of the annual total cost. Drugs accounted for nearly all treatment expenses (92.9%), followed by hospital beds, laboratory tests, diagnostic imaging, and other costs (such as procedures and medical supplies), which accounted for 2.2%, 2.0%, 2.0%, and 0.9% respectively. Regarding drug costs, HER2-targeted therapy contributed to the bulk of the total cost

(82.9%), whereas chemotherapy and other drugs (such as hormone therapy and medication to treat symptoms) comprised small portions of the total costs (6.0% and 4.0%, respectively).

Table 4 displays the variance in costs per inpatient admission according to patient characteristics. There was a statistically significant difference between the median costs of the groups concerning age, residence, occupation, and the health insurance reimbursement rate. The cost per inpatient admission of patients aged  $\geq 60$  years was the highest among the age groups. Similarly, retired patients incurred the highest costs per inpatient admission. Moreover, the median cost per inpatient admission for patients living in urban areas was higher than that for patients living in rural areas (\$740 vs. \$602). Patients with health insurance reimbursement rates of 95% and 100% had a higher median cost than patients with a rate of 80%. Other factors, such as stage of cancer and hormone receptor status did not affect the cost per inpatient admission.

**Table 4.** Cost per inpatient admission based on patient characteristics (N = 303, 2022 USD).

Characteristics	Median (IQR)	P/value
<b>Age</b>		
<40	701.3 (285.4-884.5)	<b>0.008</b>
40-49	539.1 (160.7-913.4)	
50-59	710.0 (324.7-1027.5)	
$\geq 60$	944.5 (426.5-1152.9)	
<b>Residence</b>		
Urban	753.2 (431.9-1057.6)	<b>0.009</b>
Rural	635.1 (120.6-970.6)	
<b>Occupation</b>		
Employment/Business	665.0 (373.8-867.0)	<b>&lt; 0.001</b>
Agriculture	469.3 (106.1-888.8)	
Freelancers/Housework	853.1 (531.9-1132.9)	
Retired	1004.5 (537.8-1217.3)	
<b>Social Health Insurance reimbursement rate</b>		
80%	620.4 (196.6-889.0)	<b>&lt; 0.001</b>
95%	975.2 (575.2-1215.9)	
100%	911.2 (438.7-1160.3)	
<b>Stage of cancer</b>		
I	687.0 (243.5-890.8)	0.263
II	701.7 (171.0-1032.5)	
III	714.5 (465.4-1065.7)	
<b>Hormone receptor status</b>		
Positive	690.5 (196.6-978.6)	0.184
Negative	718.6 (401.4-1033.6)	

## DISCUSSION

Our study provided the first insights into the total direct medical costs associated with adjuvant systemic treatment of HER2-positive breast cancer based on real-world data from a multicenter study in Vietnam.

Herein, the economic burden of HER2-positive breast cancer treatment was found to be substantial. Our study found that the cost per inpatient admission for systemic treatment was an average of \$680.0 (16.1 million VND), approximately 3.5 times higher than the average monthly income per person in 2022 (4.6 million VND) (General Statistics Office of Vietnam, 2022). With the significantly higher cost compared to chemotherapy alone, the combination of targeted therapy and chemotherapy may lead to a significant increase in treatment costs for HER2-positive breast cancer patients. Similarly, a patient-level data study conducted in Portugal for early breast cancer also reported that the median cost of HER2-positive breast cancer patients was four-fold higher than that of HER2-negative and triple-negative breast cancer patients who received chemotherapy regimens (Brandão et al., 2020). A separate study conducted in Japan revealed that individuals belonging to the HER2-positive category exhibited the most elevated average expenses for both overall medical care and treatment-specific costs throughout a span of 5 years (Nishikawa et al., 2024).

Currently, most chemotherapy and endocrine drugs are covered by social health insurance with a reimbursement rate of 80-100%, whereas trastuzumab is only the anti-HER2 agent that is reimbursed by health insurance at a rate of 48-60%, and other anti-HER2 agents used in adjuvant treatment such as pertuzumab are not included in benefit package of social health insurance in Vietnam (Ministry of Health, 2018). As a result, there was a considerable increase in out-of-pocket payments for patients who received regimens containing HER2-targeted therapy. Patients with regimens of the combination of chemotherapy and anti-HER2 drugs incurred \$372 (8.8 million VND) per inpatient admission. This result is roughly two times as much as the monthly income per capita of Vietnam in 2022 (4.6 million VND) (General Statistics Office of Vietnam, 2022). On the other hand, patients treated with chemotherapy regimens only paid an average of \$23.5 (0.5 million VND) per admission. These findings also emphasize the substantial financial burden on patients during the adjuvant treatment course for HER2-positive breast cancer.

In Vietnam, before initiating adjuvant systemic treatment for HER2-positive breast cancer, physicians always explained and asked the patients whether they

could afford to be treated with HER2-targeted therapy, and HER2-targeted therapies were only commenced if the patients agreed with the predicted out-of-pocket cost. Thus, 75 patients (25%) in our study could not use anti-HER2 agents because all of them were unable to pay for these drugs. This result indicates that the high cost incurred by patients may be the primary barrier limiting the accessibility of HER2-targeted therapy in Vietnam. Likewise, a survey of oncologists from the United States, Brazil, Mexico, Russia, and Turkey revealed that patient costs and insurance coverage are one of the primary obstacles to using HER2-targeted agents in an adjuvant setting (Lammers et al., 2014).

In addition, our study indicated that drug costs were responsible for 92.9% of the total spending on adjuvant systemic treatment for HER2-positive breast cancer. This finding was consistent with previous research conducted in various countries, which also found that medication expenses were the main contributors to costs at all stages of the disease (Alefan et al., 2020; Alghamdi et al., 2021; Ma et al., 2022; Mousa et al., 2021). However, the proportion of drugs in our study was much higher than that in other studies from Saudi Arabia (86%), Jordan (34.6%), and China (37.2%) (Alghamdi et al., 2021; Ma et al., 2022; Mousa et al., 2021). This difference was owing to the varying types of therapies investigated. Our study focused on the cost of systemic adjuvant treatment, whereas other studies estimated the cost of all therapies, including other therapies like surgery and radiotherapy.

We further found that HER2-targeted agents were a significant driver of cost, accounting for 82.9% of the total medication spending. This result is similar to those of several studies conducted in other countries. A study in Saudi Arabia identified targeted therapy drugs as major contributors to medication-related spending in breast cancer patients (67%) (Alghamdi et al., 2021). This was also the case in a study conducted in Jordan, where the total cost of targeted therapy accounted for almost 80.0% of medication costs (Alefan et al., 2020). The findings of our study underscore the urgent necessity to implement strategies aimed at reducing the cost of targeted therapy drugs, as these constitute the major contributors to the expenses associated with HER2-positive breast cancer. This is particularly crucial considering the limited healthcare budgets available for reimbursement. Promoting biosimilar forms of targeted therapy drugs is a potential approach to reduce their cost significantly. Biosimilars present substantial cost-saving prospects while upholding comparable effectiveness to their original counterparts, rendering them a feasible substitute (Blackwell et al., 2018; Lee et al., 2019). An alternative

strategy involves incorporating pharmacoeconomic evaluations, such as cost-effectiveness and budget impact analyses. These evaluations would be advantageous for evaluating the value and affordability of expensive drugs, as well as for optimizing the utilization of limited healthcare resources (Pallis et al., 2010). Furthermore, this can be translated into policies to reduce costs, including price negotiations. A Chinese study reported that reimbursement, price negotiations, and generic drug replacement increased the consumption of anti-HER2 drugs in Nanjing between 2012 and 2021 (Liu et al., 2022).

The cost per cycle differed among the different types of treatment cycles, and the combination of chemotherapy and targeted drugs was the most expensive. Likewise, a previous study in the United States revealed that the combination of chemotherapy (taxan, carboplatin) with the anti-HER2 agent (trastuzumab) was the most costly cycle (Giordano et al., 2016).

Some patient characteristics, including age, residence, occupation, and social health insurance reimbursement rate, affected the cost per inpatient admission. Among the age groups, patients aged 60 years and over incurred the highest cost, which was consistent with the highest cost incurred by patients who retired in our study. Two studies in China and Italy also indicated that age is highly correlated with cost per inpatient admission; however, older patients were treated at a lower cost than younger patients because of less expensive treatments and fewer follow-up tests (Capri and Russo, 2017; Ma et al., 2022). This difference between the two studies and our study was owing to the differences in the study period and the types of treatment investigated. Conversely, a previous study in Vietnam with a higher mean patient age showed no significant differences in the median total costs related to patient age groups (Hoang et al., 2013). This difference may be explained by differences in the timing of the study, treatment therapies, and stages of diagnosis. This previous study estimated the cost over 5-years. It included all treatment therapies (surgery, radiation, chemotherapy, and hormone therapy) and stages of breast cancer (early and metastatic stages). In contrast, our study analyzed the cost over one year and only focused on the adjuvant systemic treatment of patients at the early stage. Patients with a health insurance reimbursement rate of 95% and 100% had higher costs than those with a rate of 80%. In the context of the limited coverage of social health insurance for anti-HER2 agents, this result can be clarified that patients with a higher reimbursement rate may have less out-of-pocket costs. Hence, they have more affordability in using HER2-targeted therapy, which leads to an increase in costs. Likewise, a

study in China showed that patients who had medical insurance were more likely to use an anti-HER2 agent (trastuzumab) than those without medical insurance (Xia et al., 2021).

There were no statistically significant differences between the two groups in terms of hormone receptor status. This result may be attributed to the fact that hormone therapy has a low cost and was mostly used as an outpatient treatment; therefore, the cost of this therapy was not considerable during inpatient admission.

In addition, we found that the cost per inpatient admission for patients living in rural areas was lower than that for those living in urban areas. This result is probably due to the lower income. Therefore, more patients in rural areas were not affordable for targeted therapy.

This is the first study conducted in Vietnam to estimate the cost of systemic adjuvant treatment for HER2-positive breast cancer in two health facilities. These results can help substantiate the significant financial burden associated with this subtype of breast cancer and assist decision-makers in making informed choices regarding resource allocation, especially in resource-constrained settings such as Vietnam. Furthermore, our results are crucial for conducting health economic evaluations of high-cost anti-HER2 therapies.

However, this study had certain limitations. First, as patients with HER2-positive breast cancer only account for approximately 15-20% of all breast cancer patients, our sample size was not sufficiently large. Furthermore, with retrospective data from a single year, our results could not analyze the cost of a complete systemic treatment course for most patients. Since our study was conducted from the viewpoint of the entity responsible for payment, we only took into consideration the direct expenses related to medical care. We did not factor in the influence of other types of expenses, such as direct non-medical costs and indirect costs. Hence, future research should take into account the influence of both indirect and direct non-medical expenses on the overall economic load of managing HER2-positive breast cancer.

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## CONCLUSION

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The treatment of HER-positive breast cancer places a substantial financial strain on Vietnam, especially when using regimens that include HER2-targeted therapy. Drug costs, primarily comprising anti-HER2 agents, are the major driver of total direct medical costs. The findings of our study add to the increasing literature on the cost of breast cancer treatment and



can contribute to the pharmacoeconomic analysis of HER2-positive breast cancer treatment in Vietnam.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Contribution	Tram>NNL	Hang TTN	Dung XH	Quyen DTP	Thanh VT	Lan HN	Kiet THP	Chinh VN	Huong TTN
Concepts or ideas	x		x	x		x	x		x
Design	x				x	x	x		x
Definition of intellectual content	x						x		x
Literature search	x	x			x			x	
Experimental studies									
Data acquisition	x	x	x	x				x	
Data analysis	x					x			
Statistical analysis	x								
Manuscript preparation	x				x		x		x
Manuscript editing	x	x	x	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x	x	x

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