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Cost-Effectiveness of Anthracycline, Cyclophosphamide-Taxane (AC-T) Chemotherapy Based on Diagnostic Delay Status: A Payer Perspective

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ABSTRACT

Diagnostic delay in breast cancer accelerates disease progression and escalates healthcare expenditures under the National Health Insurance (Jaminan Kesehatan Nasional/JKN) program. This study aimed to evaluate the cost-effectiveness of 8-cycle anthracycline, cyclophosphamide-taxane (AC-T) chemotherapy regimen based on diagnostic delay status from the perspective of the Social Security Agency for Health (BPJS Kesehatan). A retrospective cohort study was conducted on 49 breast cancer patients at RSUP Dr. M. Djamil Padang, stratified into neoadjuvant (n = 23) and adjuvant (n = 26) arms, evaluating prospective INA-CBGs claim tariffs and serum CA 15-3 kinetics as a surrogate response biomarker. In the neoadjuvant arm, the non-delay group achieved significant within-group biomarker reduction (p = 0.007; net change: 4.69 vs. 0.31 µ/mL, between-group p = 0.231) and saved IDR 10,125,271 per patient (ICER: -IDR 2,311,706/µ/mL, dominant). In the adjuvant arm, diagnostic delay was associated with post-mastectomy biomarker elevation (-17.25 µ/mL), whereas non-delay saved IDR 10,396,936 per patient (ICER: -IDR 563,520/µ/mL, dominant). Probabilistic sensitivity analysis (10,000 iterations) confirmed 100% stability in Quadrant II of the Cost-Effectiveness Plane across both arms. Prompt diagnosis demonstrates economic dominance by curbing public reimbursement expenditures alongside favorable surrogate biomarker trajectories, supporting the macroeconomic value of strengthening early detection policies.

Keywords: Anthracycline; breast cancer; cost-effectiveness analysis; diagnostic delay; INA-CBGs

Introduction

Breast cancer represents the most prevalent malignancy and the leading cause of cancer morbidity and mortality among women globally. According to the International Agency for Research on Cancer (IARC) Global Burden of Cancer Study (GLOBOCAN) 2020, the global incidence of breast cancer reached 2,261,419 cases with 684,996 deaths. In Asia, the incidence was recorded at 1,026,171 cases with 346,009 deaths, whereas Indonesia registered 65,858 new cases and 22,430 deaths [1]. National epidemiological surveys further highlight an escalating burden, with the Basic Health Research (Riskesdas) reporting an increase in general cancer prevalence from 1.4% in 2013 to 1.49% in 2018 [2]. Among Indonesian women, breast cancer exhibits the highest incidence rate at 42.1 per 100,000 population, accompanied by an average mortality rate of 17 per 100,000 population [3].

A primary bottleneck in low- and middle-income countries (LMICs) is that the vast majority of patients are diagnosed and treated only after the disease has progressed to advanced stages. The World Health Organization (WHO) emphasizes that delayed

diagnosis and treatment contribute to 67% of cancer deaths occurring prematurely before age 70 [4]. Clinically, late-stage presentation is driven by three distinct delay dimensions: patient delay, referral delay, and treatment delay [5]. While clinical stage at initial presentation is inherently influenced by intrinsic tumor biology, molecular subtype, and proliferative aggressiveness, in real-world resource-constrained settings lacking population-based screening, initial tumor extent serves as a well-documented, pragmatic macro-level indicator, a stage based proxy for diagnostic delay [6,7]. Based on Hospital Information System (SIRS) data, the incidence of diagnostic delay in Indonesia exceeds 80%, with 60% to 70% of new patients seeking care only when the tumor has manifested as locally advanced or metastatic disease (stages IIIB-IV) [6,7]. Clinically, treatment initiation delays exceeding 12 weeks have been reported to elevated mortality risk by up to 26% [7]. Systemic management of locally advanced and high-risk early-stage breast cancer relies heavily on the standardized 8-cycle anthracycline, cyclophosphamide followed by taxane (AC-T) chemotherapy regimen [8–10] Pharmacologically, anthracyclines induce DNA intercalation and topoisomerase II inhibition, cyclophosphamide acts as an alkylating agent to disrupt DNA strand integrity, and taxanes inhibit microtubule depolymerization to arrest cell division [11,12]. Although the clinical efficacy of AC-T in achieving cytoreduction and improving disease-free survival is well established, prolonged pre-treatment lag has been associated in translational literature with uninhibited clonal diversification, the emergence of chemoresistent tumor cell phenotypes, and the estabilishment of occult micrometastases prior to therapy [11–14]. Quantifying the longitudinal kinetics of serum CA 15-3 (MUC-1 antigen) provides a sensitive, surrogate marker of real-world cytoreductive response [15–18], however, the extent to which delayed presentation impairs this biological response during AC-T therapy remains insufficiently evaluated.

From a health economics perspective, the escalation of advanced-stage oncology cases places an unprecedented financial burden on national healthcare systems [19]. In Indonesia, oncology claims reimbursed by the Social Security Agency for Health (BPJS Kesehatan) absorb trillions of Rupiah annually under the National Health Insurance (Jaminan Kesehatan Nasional/JKN) program [20]. Reimbursed through the prospective Indonesian Case-Based Groups (INA-CBGs) payment system, advanced-stage presentations inherently trigger higher severity level billing codes (severity levels II and III) due to the necessity of complex radical surgeries, extensive wound care for exophytic tumor ulcers, and prolonged inpatient episodes [21–23]. Consequently, advanced-stage presentations create a substantial economic gap, escalating claim expenditures for the public payer compared to timely early-stage management [22,23].

Although health economic evaluations of chemotherapy regimens have been conducted globally, significant knowledge gaps persist regarding the economic efficiency of diagnostic delay elimination in LMIC settings [24]. Existing local studies have evaluated generic quality of life or isolated chemotherapy costs without integrating diagnostic delay as an independent determinant, nor evaluating real-world INA-CBGs reimbursement tariffs against objective, longitudinal biomarker kinetics [25,26]. To address this gap, this study aimed to evaluate the cost-effectiveness of the 8-cycle AC-T chemotherapy regimen based on diagnostic delay status (non-delay vs. delay) from the public payer perspective (BPJS Kesehatan) in an Indonesian tertiary referral hospital, utilizing INA-CBGs prospective tariffs and serial CA 15-3 biomarker response.

METHODS

Study Design and Healthcare Perspective

This study was designed as a retrospective, real-world health economic evaluation utilizing a per-protocol cohort framework to assess the cost-effectiveness of the standadrized 8-cycles anthracycline, cyclophosphamide-taxane (AC-T) chemotherapy regimen in breast cancer management. The study adopted the public payer perspective (Payer Perspective), specifically represented by the Social Security Agency for Health (BPJS Kesehatan) under the National Health Insurance (Jaminan Kesehatan Nasional/JKN) program. Under this perspective, cost valuation was strictly restricted to direct medical expenditures reimbursed through official prospective Indonesian Case-Based Groups (INA-CBGs) claim tariffs, excluding patient out-of-pocket expenses and indirect productivity losses. The reporting of this

economic evaluation conforms to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) checklist [27]. The study was conducted at RSUP Dr. M. Djamil Padang, a top-tier regional tertiary referral hospital in West Sumatra, Indonesia, analyzing integrated clinical, administrative, and financial billing datasets spanning January 2022 to December 2024.

Patient Eligibility and Selection Pathway

The target population comprised adult female patients with histopathologically confirmed breast cancer who were indicated for and initiated on standardized AC-T regimen. The institutional cancer registry identified an initial baseline cohort of 473 breast cancer patients (N = 473) treated between 2022 and 2024. To evaluate the unconfounding biological cytoreductive response and full reimbursement trajectory of the completed protocol, a multi-stage eligibility screening was executed (**Figure 1**). A total of 424 patients were excluded based on predefined criteria: 168 patients lacked complete baseline or serial post-chemotherapy CA 15-3 laboratory tracking; 118 discontinued treatment prematurely due to intolerable hematologic/non-hematologic toxicities or loss to follow up; 87 experienced early clinically disease progression requiring emergency regimen switching; and 51 presented with synchronous secondary malignancies that confounded biomarker specificity and billing attribution. Consequently, the final analytic per-protocol cohort comprised 49 subjects (N = 49).

To account for clinical and sequence heterogeneity, patients were stratified into neoadjuvant (preoperative chemotherapy, n = 23) and adjuvant (post-chemotherapy, n = 26) management arm. In the adjuvant cohort, the inclusion of select Stage IV patients reflected real-word tertiary clinical practice in LMICs, were patients presenting with fungating, bleeding, or infected exophytic tumors underwent upfront palliative toilet mastectomy for local symptom control prior to systemic adjuvant chemotherapy. All enrolled patients completed the full 8-cycle AC-T protocol (4 cycles of doxorubicin-cyclophosphamide followed by 4 cycles of taxane) in accordance with the National Comprehensive Cancer Network (NCCN) guidelines [28]. Complete clinicopathological profiles were required, including estrogen receptor (ER) and progesterone receptor (PR) nuclear positivity (≥1%) per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines [29,30], Ki-67 proliferation index categorized at a 20% cut-off per St. Gallen International Consensus guidelines [31], HER2 status, and intrinsic molecular subtypes.

Study Variables and Operational Definitions

The primary exprosure variable was the diagnostic delay status, operationalized using the American Joint Committee on Cancer (AJCC) 8th edition clinical TNM stage at initial hospital encounter as a validated stage-based proxy for diagnostic delay [32]. In resource-constrained settings lacking population-based screening, initial clinical stage strongly reflects cumulative pre-hospital diagnostic lag: patients presenting at early-to-locally advanced stages (TNM stages 0-IIIA) were classified into the non-delay group, whereas those presenting at advanced/metastatic stages (TNM stages IIIB-IV) were categorized into the delay group. Recorded sociodemographic variables included age, educational attainment, occupational status, and marital status. Clinicopathological covariates included tumor laterality, primary tumor extent (T stage), regional nodal involvement (N stage), distant metastasis (M stage), hormonal receptor status, Ki-67 index, and molecular subtypes (Luminal A, Luminal B, Basal-like/TNBC, and HER2-enriched).

Cost Valuation and Clinical Outcome Parameters

Cost valuation was conducted from official electronic claim reimbursement files extracted from the Hospital Management Information System (SIM-RS), verified by the hospital's Insurance and Health Verification Unit. Direct medical costs were defined as the cumulative prospective reimbursement paid by BPJS Kesehatan to the hospital for 8 complete AC-T cycles, primary surgical resection (modified radical mastectomy or toilet mastectomy), inpatient accommodation, diagnostics monitoring, and supportive medications based on the 2023/2024 national prospective tariff regulation (Minister of Health Regulation No. 3/2023) [33]. Costs represent public payer tariffs rather than hospital provider micro-costs, The

analytic time horizon was episode-based, convering the active treatment duration (~6 months); therefore, cost discounting and annual inflation adjustments were not required. To facilitate international comparisons and meta-analyses, all costs are reported in both Indonesian Rupiah (IDR) and Purchasing Power Parity Internasional Dollars ($PPP), using the World Bank PPP conversion factor for Indonesia ($1 USD PPP = IDR 5,100).

Clinical efficacy was operationalized as an exploratory surrogate endpoint: the net change in serum CA 15-3 biomarker concentration (ΔEffect in μ/mL), measured within 7 days prior to Cycle 1 and within 14 days following Cycle 8 completion. ΔEffect was calculated as baseline CA 15-3 minus post-chemotherapy CA 15-3, Where a positive delta signifies tumor cytoreduction and a negative delta denotes biomarker progression.

Economic Modeling and Sensitivity Analyses

An exploratory Cost-effectiveness analysis (CEA) was excuted separately for the neoadjuvant and adjuvant arms. Incremental cost-effectiveness was evaluated using the Incremental Cost-Effectiveness Ratio (ICER):

$$\text{ICER} = \frac{\text{Mean cost non} - \text{delay} - \text{Mean cost delay}}{\text{Mean effect non} - \text{delay} - \text{Mean effect delay}} = \frac{\Delta\text{Cost}}{\Delta\text{Effect}}$$

Results were plotted on the Cost-Effectiveness Plane (CE-Plane), where placement in Quadrant II (negative ΔCost and positive ΔEffect) denotes absolute economic dominance (cost-saving and superior efficacy).

To addres parameter uncertainty, two-tiered sensitivity analyses were conducted using TreeAge Pro. One-Way Deterministic Sensitivity Analysis (DSA) evaluated the impact of individual parameters variation across their 95% confidence intervals (95% CI), visualized via Tornado Diagrams. Probabilistic Sensitivity Analysis (PSA) was executed using 10,000 Monte Carlo simulation iterations. Costs were sampled from Gamma distributions (parameterized by mean and standard error) to accommodate both positive reduction and negative biomarker surges.

Statistical Analysis and Ethical Approval

Continuous data were assessed for normality using the Shapiro-Wilk test. Differences in serial CA 15-3 biomarker levels pre- and post-chemotherapy were evaluated using the non-parametric Wilcoxon Signed-Rank test. Mean differences in INA-CBGs tariffs between non-delay and delay groups were analyzed using the Independent Student's t-test for normally distributed data (neoadjuvant arm) and the Mann-Whitney U test for non-normally distributed data (adjuvant arm). All statistical computations were performed using IBM SPSS Statistics for Windows, Version 31.0 (IBM Corp., Armonk, NY, USA), with two-tailed significance set at $p < 0.05$. This study fully complied with national and international ethical standards according to the Declaration of Helsinki. Ethical approval was granted by the Health Research Ethics Committee of RSUP Dr. M. Djamil Padang under Protocol Registration Number DP.04.03/D.XVI.XI/71/2024. Operational research permits were formally issued by the Research and Development Division of RSUP Dr. M. Djamil Padang for legal access to integrated SIM-RS electronic health databases and physical medical records.

RESULT AND DISCUSSION

Baseline Sociodemographic and Clinicopathological Profiles

Evaluation of baseline sociodemographic and clinicopathological profiles among the 49 analyzed patients (N = 49) revealed a predominant representation of women under 50 years of age (53.1%), individuals with primary education (34.7%), and housewives (77.6%), as detailed in **Table 1**.

Table 1. Comparison of pre-chemotherapy and post-chemotherapy serum CA 15-3 levels following 8 cycles of AC-T chemotherapy based on diagnostic delay status (N=49)

Clinicopathologic characteristic	n (%)	CA15-3 Baseline (μ/mL)						p-Value
		Min	Max	Mean	SD	< 30 μ/mL n (%)	≥ 30 μ/mL n (%)	
Age (years)								
< 50	26 (53.1)	4.10	327.11	33.50	63.27	21 (42.9)	5 (10.2)	0.194a
≥ 50	23 (46.9)	5.64	36.12	17.86	7.86	22 (44.9)	1 (2.0)	
Education level								
Elementary school	17 (34.7)	6.78	104.52	21.72	22.42	15 (30.6)	2 (4.1)	0.919b
Junior high school	6 (12.2)	5.64	327.11	66.61	127.88	5 (10.2)	1 (2.0)	
Senior high school	13 (26.5)	6.48	37.18	20.84	9.71	11 (22.4)	2 (4.1)	
University/College	13 (26.5)	4.10	56.97	18.63	13.60	12 (24.5)	1 (2.0)	
Occupation								
Housewives	38 (77.6)	5.64	327.11	28.40	52.76	32 (65.3)	6 (12.2)	0.315a
Civil servant	11 (22.4)	4.10	26.54	18.42	7.49	11 (22.4)	0 (0)	
Marital state								
Merried	41 (83.7)	4.10	327.11	26.82	50.69	36 (73.5)	5 (10.2)	1.000a
Single	8 (16.3)	10.23	56.97	22.78	14.68	7 (14.3)	1 (2.0)	
Tumor Laterality								
Left	23 (46.9)	5.64	36.12	17.87	8.09	22 (44.9)	1 (2.0)	0.249b
Right	20 (40.8)	4.10	327.11	38.21	71.64	16 (32.7)	4 (8.2)	
Bilateral	6 (12.2)	8.86	36.15	17.76	10.48	5 (10.2)	1 (2.0)	
Tumor Stage								
Tis	4 (8.2)	8.78	17.54	11.47	4.08	4 (8.2)	0 (0)	0.146b
T1	1 (2.0)	36.12	36.12	36.12	N/A	0 (0)	1 (2.0)	
T2	3 (6.1)	4.10	13.67	10.41	5.47	3 (6.1)	0 (0)	
T3	24 (49.0)	6.78	56.97	18.55	10.77	22 (44.9)	2 (4.1)	
T4	17 (34.7)	5.64	327.11	42.56	76.63	14 (28.6)	3 (6.1)	
Nodul Stage								
N0	14 (28.6)	4.10	36.15	16.54	10.11	12 (24.5)	2 (4.1)	0.503b
N1	8 (16.3)	6.78	104.52	26.68	32.41	7 (14.3)	1 (2.0)	
N2	19 (38.8)	6.48	327.11	36.94	71.18	16 (32.7)	3 (6.1)	
N3	8 (16.3)	8.67	28.94	16.89	6.81	8 (16.3)	0 (0)	

Table 1. Comparison of pre-chemotherapy and post-chemotherapy serum CA 15-3 levels following 8 cycles of AC-T chemotherapy based on diagnostic delay status (N=49)

Clinicopathologic characteristic	n (%)	CA15-3 Baseline (μ/mL)						p-Value
		Min	Max	Mean	SD	< 30 μ/mL n (%)	≥ 30 μ/mL n (%)	
Metastasis Stage								
Mx	3 (6.1)	9.34	23.38	14.98	7.41	3 (6.1)	0 (0)	0.267b
M0	34 (69.4)	4.10	104.52	19.67	16.99	31 (63.3)	3 (6.1)	
M1	12 (24.5)	5.64	327.11	47.35	89.23	9 (18.4)	3 (6.1)	
TNM stage								
0	2 (4.1)	10.23	17.54	13.88	5.16	2 (4.1)	0 (0)	0.192b
IA	1 (2.0)	36.12	36.12	36.12	N/A	0 (0)	1 (2.0)	
IIA	1 (2.0)	4.10	4.10	4.10	N/A	1 (2.0)	0 (0)	
IIB	7 (14.3)	9.23	36.15	18.41	9.54	6 (12.2)	1 (2.0)	
IIIA	9 (18.4)	6.78	26.54	16.34	7.32	9 (18.4)	0 (0)	
IIIB	11 (22.4)	6.48	104.52	25.17	27.06	10 (20.4)	1 (2.0)	
IIIC	5 (10.2)	11.51	28.94	16.72	7.10	5 (10.2)	0 (0)	
IV	13 (26.5)	5.64	327.11	44.42	86.08	10 (20.4)	3 (6.1)	
ER								
Positive	27 (55.1)	5.64	56.97	19.91	11.29	24 (49.0)	3 (6.1)	1.000a
Negative	22 (44.9)	4.10	327.11	33.84	68.57	19 (38.8)	3 (6.1)	
PR								
Positive	27 (55.1)	5.64	56.97	19.91	11.29	24 (49.0)	3 (6.1)	1.000a
Negative	22 (44.9)	4.10	327.11	33.84	68.57	19 (38.8)	3 (6.1)	
Ki-67 (%)								
≥ 20	36 (73.5)	4.10	327.11	26.78	52.35	33 (67.3)	3 (6.1)	0.321a
< 20	13 (26.5)	5.64	104.52	24.44	26.50	10 (20.4)	3 (6.1)	
Molecular subtype								
Luminal A	10 (20.4)	5.64	37.18	18.00	12.49	8 (16.3)	2 (4.1)	0.127b
Luminal B	18 (36.7)	9.34	56.97	21.21	10.47	17 (34.7)	1 (2.0)	
Basal-Like	20 (40.8)	4.10	327.11	30.79	70.14	18 (36.7)	2 (4.1)	
Her2-enriched	1 (2.0)	104.52	104.52	104.52	N/A	0 (0)	1 (2.0)	
TNBC								
Yes	22 (44.9)	4.10	327.11	33.84	68.57	19 (38.8)	3 (6.1)	1.000a
No	27 (55.1)	5.64	56.97	19.91	11.29	24 (49.0)	3 (6.1)	

Table 1. Comparison of pre-chemotherapy and post-chemotherapy serum CA 15-3 levels following 8 cycles of AC-T chemotherapy based on diagnostic delay status (N=49)

Clinicopathologic characteristic	n (%)	CA15-3 Baseline (μ/mL)						p-Value
		Min	Max	Mean	SD	< 30 μ/mL n (%)	≥ 30 μ/mL n (%)	
Grade								
I	2 (4.1)	9.23	11.69	10.46	1.73	2 (4.1)	0 (0)	0.712b
II	28 (57.1)	6.48	327.11	33.07	60.70	24 (49.0)	4 (8.2)	
III	19 (38.8)	4.10	37.18	17.62	9.70	17 (34.7)	2 (4.1)	
Surgery								
Post-MRM	41 (83.7)	4.10	327.11	27.18	50.89	36 (73.5)	5 (10.2)	1.000a
Pre-MRM	8 (16.3)	12.23	36.12	22.64	7.54	7 (14.3)	1 (2.0)	
Chemotherapy Management Scheme								
Neoadjuvant	23 (46.9)	5.64	104.52	22.62	19.47	21 (42.9)	2 (4.1)	0.671a
Adjuvant	26 (53.1)	4.10	327.11	29.30	61.81	22 (44.9)	4 (8.2)	
Diagnosis Delay Status								
Delay (stadium: IIIB, IIIC, IV)	29 (59.2)	4.1	36.15	17.19	9.09	25 (51.0)	4 (8.2)	1.000a
Non-delay (stadium: 0–IIIA)	20 (40.8)	5.64	327.11	32.34	59.80	18 (36.7)	2 (4.1)	

Min: minimal; Max: maximal; SD: standard deviation; TNM: tumor, node, metastasis; ER: estrogen receptor; PR: progesteron receptor; TNBC: triple negative breast cancer; MRM: modified radical mastectomy; N/A: not applicable; a: Fisher's Exact Test; b: Likelihood Ratio.

Clinicopathological indicators demonstrated a substantial burden of advanced disease at initial tertiary encounter, evidenced by the high proportions of T3 primary tumor size (49.0%), N2 regional lymph node involvement (38.8%), non-metastatic M0 status (69.4%), and stage IV presentation (26.5%). Hormonal biomarker profiling showed a dominance of estrogen receptor (ER)-positive (55.1%), progesterone receptor (PR)-positive (55.1%), high Ki-67 proliferation index ≥ 20% (73.5%), and the Basal-like intrinsic molecular subtype (40.8%). Baseline characteristics stratified by diagnostic delay status (non-delay vs. delay) demonstrated broadly comparable clinicopathological distributions. Baseline serum CA 15-3 concentrations exhibited wide interindividual variability across the cohort (range 4.10 to 327.11 μ/mL; overall mean: 31.42 ± 53.76 μ/mL) Bivariate analyses demonstrated no statistically significant association between baseline sociodemographic or clinicopathological categories and baseline serum CA 15-3 cut-off threshold (< 30 μ/mL vs. ≥ 30 μ/mL, $p > 0.05$). The substantial baseline heterogeneity reflects variable MUC-1 antigen shedding during initial tumor development [14], supporting the premise that baseline CA 15-3 lacks diagnostic utility as cross-sectional screening tool but serves as an exploratory personal monitoring parameter when evaluated longitudinally during systemic therapy [34–39].

Table 2. Comparison of pre-chemotherapy and post-chemotherapy serum CA 15-3 levels following 8 cycles of AC-T chemotherapy based on diagnostic delay status (N=49)

Chemotherapy Management Scheme		CA 15-3 (μ/mL)								p-Value
		Pre-chemotherapy				Post-chemotherapy				
		Min	Max	Mean	SD	Min	Max	Mean	SD	
Neoadjuvant	Delay (n = 14)	5,64	104,5	24,18	24,31	5,76	96,82	23,87	23,12	0,910
	Non-delay (n = 9)	8,86	36,12	20,19	8,48	5,3	34,38	15,5	8,35	0,007*
Adjuvant	Delay (n = 15)	6,48	327,1	39,97	80,46	6,62	351,16	57,22	102,41	0,281
	Non-delay (n = 11)	4,1	36,15	14,75	9,21	3,5	34,21	13,55	9,19	0,131

Clinical Efficacy and Biomarker Dynamics

Longitudinal evaluation of surrogate serum CA 15-3 kinetics following 8 complete cycles of AC-T chemotherapy revealed distinct exploratory trajectories across diagnostic status group, as summarized in **Table 2**. Within the neoadjuvant arm, the non-delay group (n = 9) demonstrated a statistically significant within-group reduction in mean serum CA 15-3 concentration from 20.19 ± 8.48 μ/mL pre-chemotherapy to 15.50 ± 8.35 μ/mL post-chemotherapy (Wilcoxon signed-rank test, p = 0.007). Conversely, the neoadjuvant delay group (n = 14) exhibited an essentially unchanged biomarker trajectory, moving from 24.18 ± 24.31 μ/mL to 23.87 ± 23.12 μ/mL (p = 0.910). In adjuvant arm, paired within-group alterations did not reach statistical significance in either non-delay (n = 11, 19.55 ± 10.96 to 18.35 ± 8.47 μ/mL, p = 0.131) or delay (n = 15, 39.97 ± 80.46 to 57.22 ± 102.41 μ/mL, p = 0.281) subgroups.

Evaluating net biomarker changes (**Table 3**), the neoadjuvant non-delay group achieved a mean CA 15-3 reduction of 4.69 μ/mL compared to 0.31 μ/mL in the delay group; however, this between group difference did not reach formal statistical significance (Mann-Whitney U test, p = 0.231). In the adjuvant arm, the non-delay group showed a modest mean reduction of 1.20 μ/mL, whereas the delay group exhibited a paradoxical negative mean change of -17.25 μ/mL due to post-mastectomy biomarker increases in select patients, though this between-group difference was likewise not statistically significant (p = 0.287). In translational oncology literature, post-surgical biomarker elevations are hypothesized to chemoresistant sub-clones [40–42]. Prolonged diagnostic delays provide an extended time window for cancer cells to acquire secondary genetic mutations and establish systemic distant niches before primary surgical extirpation, rendering chemotherapy less effective [43–45]. Nevertheless, given the small sample sizes (n = 9–15 per subgroup) and lack of between-group statistical significance, these biomarker patterns should be interpreted cautiously as exploratory clinical signals rather than definitive proof of therapeutic failure.

Direct Medical Costs and Payer Reimbursement Analysis

Direct medical cost analysis based on official prospective INA-CBGs claim tariffs demonstrated that advanced-stage delayed presentations were associated with higher public payer expenditures, as detailed in **Table 4**. In the neoadjuvant arm, average claim reimbursements were IDR 54,098,737.86 ± 13,104,382.40 ($10,607.60 PPP) for the delay group compared to IDR 43,973,466.67 ± 17,265,326.40 ($8,622.25 PPP) for the non-delay group, reflecting an observed incremental cost difference (ΔCost) of -IDR 10,125,271.19 (-$1,985.35 PPP) per patient, which approached but did not achieve statistical significance (independent Student's t-test, p = 0.062). In the adjuvant arm, mean reimbursement was IDR 55,120,791.00 ± 14,278,961.90 ($10,808.00 PPP) in the

Table 3. Mean changes in serum CA 15-3 levels (ΔEffect) post-AC-T 8-cycle chemotherapy in neoadjuvant and adjuvant arms (N = 49)

Chemotherapy Management Scheme		CA15-3 (μ/mL) Chemotherapy		Average Change Value of CA 15-3 (μ/mL)	Change Status of CA 15-3	p-Value
		Pre Mean	Post Mean			
Neoadjuvant	Delay (n = 14)	24.18	23.87	0.31	Decreased	0.231
	Non-delay (n = 9)	20.19	15.5	4.69	Decreased	
Adjuvant	Delay (n = 15)	39.97	57.22	-17.25	Increased	0.287
	Non-delay (n = 11)	14.75	13.55	1.20	Decreased	

Table 4. Base-case Incremental Cost-Effectiveness Rasio (ICER) metrics for 8-cycle AC-T chemotherapy regimen based on diagnostic delay status (N = 49)

Chemotherapy Management Cheme	Diagnostic Delay Status Group	n	Total Rate INA-CBGs (IDR, Mean ± SD)	Confidence Interval (95% CI)	Incremental Cost (Δ Cost, IDR)	p-Value
Neoadjuvan	Delay	14	54,098,737.86 ± 13,104,382.4	46,532,492.71 – 61,664,983.01	-10,125,271.19	0.062
	Non-delay	9	43,973,466.67 ± 17,265,326.4	30,702,162.00 – 57,244,771.33		
Adjuvan	Delay	15	55,120,791.00 ± 14,278,961.9	47,213,365.49 – 63,028,216.51	-10,396,936.45	0.065
	Non-delay	11	44,723,854.55 ± 18,113,548.1	32,555,007.38 – 56,892,701.38		

Table 5. Base-case Incremental Cost-Effectiveness Rasio (ICER) metrics for 8-cycle AC-T chemotherapy regimen based on diagnostic delay status (N = 49)

Chemotherapy Management Cheme	Diagnostic Delay Status Group	Mean Total Rate INA-CBGs (IDR)	Δ Cost (IDR)	Mean Change CA 15-3 (μ/mL)	Δ Effect (μ/mL)	ICER Value (IDR/μ/mL)
Neoadjuvan	Delay (n = 14)	54,098,737.86	-10,125,271.19	0.31	4.38	-2,311,705.75 Strongly Dominant (Quadrant II)
	Non-delay (n = 9)	43,973,466.67		4.69		
Adjuvan	Delay (n = 15)	55,120,791.00	-10,396,936.45	-17.25	18.45	-563,519.59 Strongly Dominant (Quadrant II)
	Non-delay (n = 11)	44,723,854.55		1.20		

delay group versus IDR 44,723,854.55 ± 18,113,548.10 ($8,769.38 PPP) in the non-delay group, generating an incremental cost difference of -IDR 10,396,936.45 (-$2,038.62 PPP) per patient (Mann-Whitney U test, p = 0.065). Under the INA-CBGs prospective case-mix system, delayed advanced-stage cases (stages IIIB–IV) frequently require extensive surgical interventions (e.g., modified radical mastectomy with complete axillary clearance or palliative ulcer debridement) and prolonged hospitalizations that trigger higher severity level billing codes (severity levels II and III), explaining the observed cost disparity.

Incremental Cost-Effectiveness and CE-Plane Analysis

Synthesizing incremental reimbursement cost and exploratory clinical biomarker responses into the Incremental Cost-Effectiveness Ratio (ICER) identified prompt diagnostic management (non-delay) as a dominant strategy within this cohort as summarized in **Table 5**. In the neoadjuvant setting, the non-delay strategy yielded observed cost savings (ΔCost = -IDR 10,125,271.19/-$1,985.35 PPP) alongside numerically greater biomarker cytoreduction (ΔEffect = +4.38 μ/mL), resulting in a dominant base-case ICER of -IDR 2,311,705.75/μ/mL (-$453.28 PPP/μ/mL). In the adjuvant setting, non-delay was associated with cost savings (ΔCost = -IDR 10,396,936.45 / -$2,038.62 PPP) and prevention of biomarker surge (ΔEffect = +18.45 μ/mL), producing a dominant ICER of -IDR 563,519.59/μ/mL (-$110.50 PPP/μ/mL).

When plotted on the Cost-Effectiveness Plane (**Figure 2**), base-case coordinates for both the neoadjuvant arm (ΔEffect = 4.38 μ/mL; ΔCost = -IDR 10.13 million) and adjuvant arm (ΔEffect = +18.45 μ/mL; ΔCost = -IDR 10.40 million) were positioned within Quadrant II (bottom-right quadrant: cost-saving and more effective). Positioning in Quadrant II indicates economic dominance within the framework of this exploratory model, obviating the requirement for an explicit willingness-to-pay (WTP) threshold comparison.

Deterministic and Probabilistic Sensitivity Analyses

To evaluate the resilience of the base-case economic conclusions against single-parameter fluctuations, One-Way Deterministic sensitivity analysis

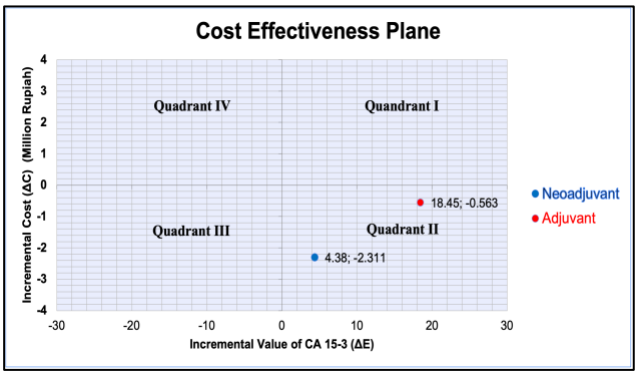

Figure 2. Cost effectiveness plane (CE Plane) metrics base case analysis of the AC-T regimen use based on change effectiveness of CA 15-3 and INA-CBGs rates (perspektif payer).

(DSA) was executed across the 95% confidence intervals (95% CI) and visualized through Tornado Diagrams for the neoadjuvant (**Figure 3**) and adjuvant (**Figure 4**) chemotherapy arms. The hierarchial structure of the tornado diagrams revealed distinct mechanisms driving parameter uncertainty across the two clinical settings, reflecting the interplay between tumor biology and prospective reimbursement mechanics.

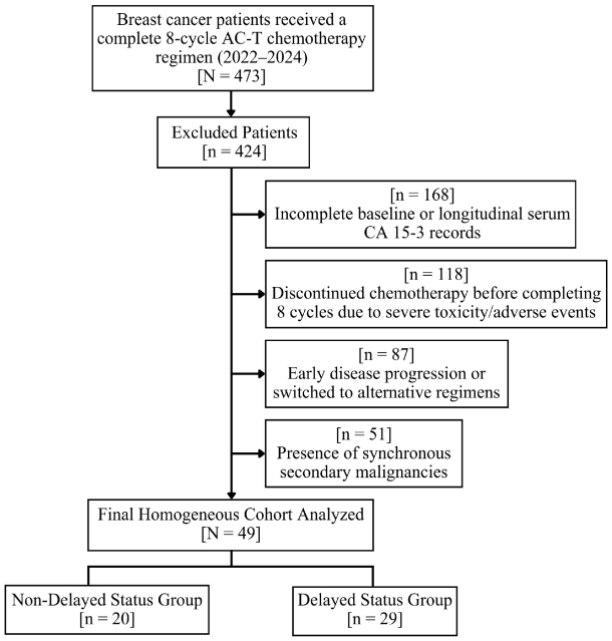

Figure 1. Flowchart of patient screening, attrition pathways, and cohort stratification. AC-T: doxorubicin-cyclophosphamide followed by a taxane; CA 15-3: cancer antigen 15-3. Non-delay and delay groups were categorized based on clinical stage at initial presentation as a proxy for diagnostic delay status.

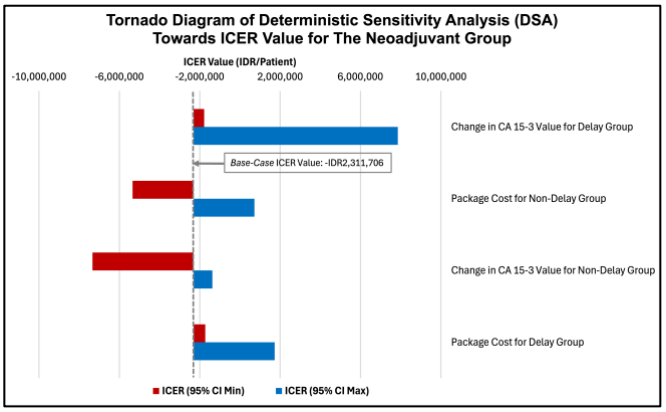

Figure 3. Tornado diagram of deterministic sensitivity analysis-DSA towards ICER value for The neoadjuvant chemotherapy group.

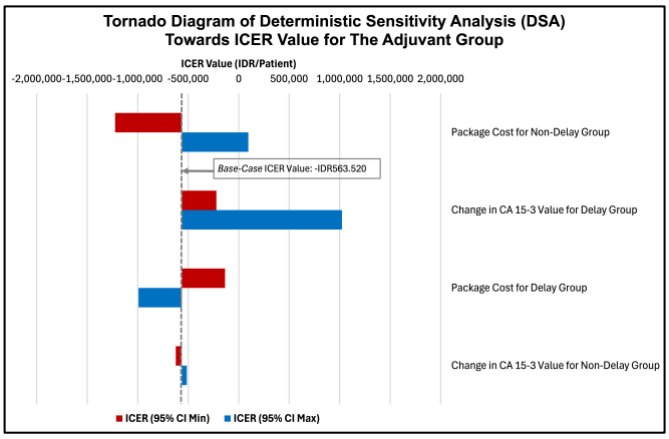

Figure 4. Tornado diagram of deterministic sensitivity analysis-DSA towards ICER value for the adjuvant chemotherapy group.

In the neoadjuvant setting (**Figure 3**), where the base-case ICER was established at-IDR 2,311,706/μ/mL, the tornado diagram demonstrated that the clinical efficacy change in serum CA 15-3 within the delay group was the most influential parameter governing ICER volatility. Variations across its 95% CI generated the widest horizontal swing, spanning from -IDR 1,600,000 to approximately +IDR 8,000,000/ μ/mL. This pronounced sensitivity is biologically rooted in the extensive tumor burden and cellular heterogeneity of advanced- stage presentations (stages IIIB-IV). In delayed patients, prolonged pre-treatment lag fosters clonal diversification and drug resistance, resulting in marked interindividual variation in preoperative cytoreduction. Because this biological variance directly alters the denominator (ΔEffect) in the ICER equation, shifts in CA 15-3 reduction in the delay group exert substantial leverage on the cost-effectiveness ratio. The secondary and tertiary drivers of uncertainty were the prospective package tariff for the non-delay group (ranging from -IDR 5,500,000 to +IDR 1,000,000/μ/mL) and the CA 15-3 change in the non-delay group (ranging from -IDR 7,500,000 to -IDR 1,400,000/μ/mL), while the package cost for the delay group had a moderate impact.

Conversely, the adjuvant chemotherapy setting (**Figure 4**), characterized by a base-case ICER of -IDR 563,520/μ/mL, exhibited a distinct uncertainty profile. The prospective package tariff of the non-delay group emerged as the primary determinant of ICER fluctuation, spanning from -IDR 1,200,000 to approximately +IDR 150,000/μ/mL. This transition from biological to financial drivers is clinically plausible: following primary surgical resection (modified radical mastectomy), macroscopic tumor mass is removed, standardizing subsequent systemic chemotherapy delivery. Consequently, post-surgical biomarker kinetics exhibit lower absolute variance compared to in situ neoadjuvant settings, shifting sensitivity toward the numerator (ΔCost). Under the INA-CBGs prospective payment system, variations in base-case hospitalization and severity coding for early-stage cases directly determine the magnitude of payer cost savings. The second most sensitive parameter in the adjuvant arm was the CA 15-3 change in the delay group (ranging from -IDR 200,000 to +IDR 1,000,000/μ/mL), driven by post-mastectomy biomarker surges (-17.25 μ/mL), followed by the delay package tariff and non-delay biomarker reduction.

Although extreme 95% CI upper-bound parameter permutations shifted the ICER across the vertical zero-axis into positive values (reaching up to +IDR 8,000,000/μ/mL in neoadjuvant and +IDR 1,000,000/μ/mL in adjuvant settings), these maximum values remain exceptionally modest and economically justifiable relative to national macroeconomic thresholds (~IDR 75–225 million per capita benchmark). This demonstrates that prompt diagnostic management (non-delay) maintains structural economic superiority and robust decision stability across diverse clinical and reimbursement scenarios.

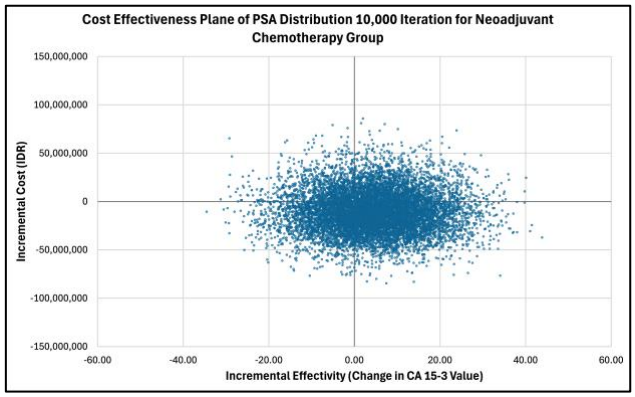

Figure 5. Cost Effectiveness Plane of PSA Distribution 10,000 Iteration Based on INA-CBGs Rates for The Neoadjuvant Group.

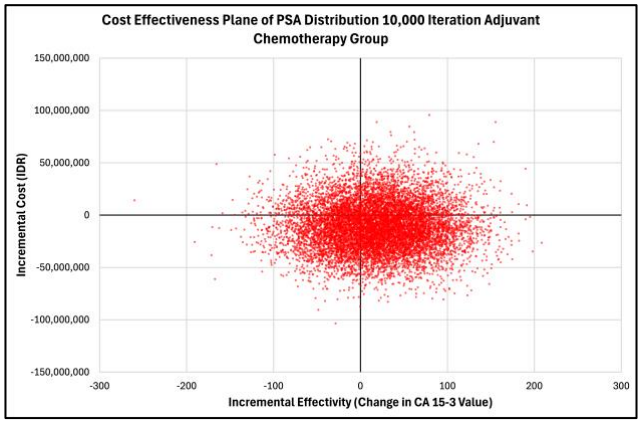

Figure 6. Cost Effectiveness Plane of PSA Distribution 10,000 Iteration Based on INA-CBGs Rates for The Adjuvant Group.

Probabilistic Sensitivity Analysis and Decision Certainly

To evaluate simultaneous joint parameter uncertainty across clinical and financial inputs, a Probabilistic sensitivity analysis (PSA) was executed using a 10,000-iteration Monte Carlo simulation. Direct medical costs (INA-CBGs claim tariffs) were parameterized using Gamma distributions to accommodate the inherent right-skewness and strictly non-negative distribution of hospital reimbursement data, while clinical efficacy changes (ΔEffect) were modeled using Normal and Beta distributions to capture continuous biomarker variation. The simulation outputs are plotted on the Cost-Effectiveness Planes in **Figure 5** (neoadjuvant arm) and **Figure 6** (adjuvant arm).

Across both clinical cohorts, the stochastic simulation demonstrated exceptional model stability. Specifically, 10,000 out of 10,000 simulated iterations (100% probabilistic certainty) congregated exclusively within Quadrant II (the bottom-right quadrant: negative ΔCost and positive ΔEffect). In the neoadjuvant setting (**Figure 5**), the scatter cloud displayed a tight elliptical aggregation below the cost-neutral horizontal axis (ΔCost = 0), confirming consistent prospective claim savings paired with predictable preoperative cytoreduction. In the adjuvant setting (**Figure 6**), the simulated coordinate cloud demonstrated wider horizontal dispersion along the ΔEffect axis, reflecting the biological heterogeneity of post-mastectomy residual disease and occult micrometastases in delayed cases. Nevertheless, all 10,000 adjuvant iterations remained strictly beneath the horizontal zero-cost axis, reaffirming that prompt diagnosis consistently reduces public payer expenditure regardless of patient-level variation. In health technology assessment (HTA), a 100% point concentration in Quadrant represents absolute stochastic dominance. This positioning establishes that the probability of prompt diagnosis being cost-effective reaches 1.0 (100%) even at a Willingness-to-Pay (WTP) threshold of IDR 0, which obviates the necessity of presenting conventional Cost-Effectiveness Acceptability Curves (CEAC). From a health policy standpoint, this complete absence of decision uncertainty provides definitive assurance to the national health insurance agency (BPJS Kesehatan) and the Ministry of Health that eliminating diagnostic delay carries zero risk of financial decision reversal. Consequently, allocating public resources toward community-based breast self-examination (SADARI), clinical breast examination (SADANIS), and streamlined primary-to-tertiary fast-track referral pathways is substantiated not merely as a clinical priority, but as a dominant, cost-saving macroeconomic intervention for the national healthcare system [46,47].

Study Limitations and Policy Implications

Several important methodological and clinical limitations must be acknowledged. First, the modest sample size (N = 49; n = 9–15 per subgroup) reduced statistical power, precluding multivariable econometric regression to control for potential residual confounding (such as specific patient comorbidities, performance

status, or post-surgical wound complications). Second, the strict per-protocol design, which excluded patients who experienced severe toxicities, early disease progression, or treatment discontinuation, introduces inherent selection and survivorship bias; thus, findings reflect outcomes among patients capable of completing full curative-intent chemotherapy. Third, the use of initial clinical stage as a proxy for diagnostic delay carries the risk of exposure misclassification, as stage reflects both health-seeking lag time and intrinsic biological aggressiveness. Fourth, serum CA 15-3 is an exploratory surrogate biomarker rather than a final patient-centered outcome (such as quality-adjusted life years [QALYs] or overall survival). Fifth, cost valuation reflected prospective INA-CBGs reimbursement tariffs from the public payer perspective at a single tertiary center in West Sumatra, which may not capture true provider micro-costs or generalize directly to secondary hospital settings.

Notwithstanding these constraints, our findings demonstrate that delayed, advanced-stage presentations place a substantial economic burden on the national health insurance system under prospective case-based payment mechanisms. Promoting early clinical detection (SADARI and SADANIS) and expediting referral pathways may offer meaningful health economic value by reducing high-severity claim expenditures and optimizing public healthcare resource.

CONCLUSION

This study demonstrates that prompt diagnostic management (non-delay status) in breast cancer patients receiving the standardized 8-cycle AC-T chemotherapy regimen is a strongly dominant healthcare strategy from the public payer perspective (BPJS Kesehatan). In the primary incremental economic evaluation, eliminating diagnostic delay achieved superior clinical efficacy, securing statistically significant preoperative tumor cytoreduction in the neoadjuvant setting ($p = 0.007$) and preventing post-mastectomy biomarker surges in the adjuvant setting, while delivering substantial prospective claim cost saving exceeding IDR 10 million per patient. Consequently, the base-case Incremental Cost-Effectiveness Ratio (ICER) positioned the non-delay strategy squarely within Quadrant II (dominant: cost-saving and more effective) on the Cost-Effectiveness Plane for both neoadjuvant (ICER: -IDR 2,311,706/μ/mL) and adjuvant (ICER: -IDR 563,520/μ/mL) arms, backed by 100% probabilistic certainty under Monte Carlo simulation.

While preliminary Average Cost-Effectiveness Ratio (ACER) calculations provided baseline cost-per-outcome estimates, the ICER framework served as the definitive decision-making metric by overcoming the inherent interpretation bias of ACER during therapeutic failure. These real-world pharmacoeconomic findings substantiate the critical urgency of strengthening and financing nationwide breast cancer early detection strategies, particularly community-based breast self-examination (SADARI), clinical breast examination (SADANIS), and streamlined primary-to-tertiary fast-track referral pathways. Investing in early diagnosis functions not only as a clinical necessity to prevent disease progression but also as a high-value, cost-saving macroeconomic intervention that preserves national health insurance sustainability.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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