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Medication Persistence in Heart Failure with Coronary Artery Disease: A Pharmacoeconomic Analysis of Cost-Effectiveness and Cost-Drivers in Indonesia

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ABSTRACT

Heart failure (HF) secondary to coronary artery disease (CAD) imposes a severe clinical and economic burden in low- and middle-income countries (LMICs). This study evaluated the 30-day medication persistence rate, its independent predictors, and its pharmacoeconomic impact from the hospital provider perspective in Indonesia. A retrospective cohort study was conducted using integrated electronic medical records from UNS Hospital (2022–2023), encompassing 284 patients hospitalized for CAD-related HF. Medication persistence was operationally defined using the Ascertaining Barriers for Compliance (ABC) taxonomy as documented pharmacy refill claims within days 25–35 post-discharge. Pharmacoeconomic evaluations included Cost-Effectiveness Analysis (CEA), Cost-Minimization Analysis (CMA) with matched clinical outcomes, bivariate correlation analysis, and log-linear multivariate regression to identify independent cost drivers. Only 13.7% (n=39) of patients achieved medication persistence at 30 days. Multivariate logistic regression revealed that the absence of kidney disease (OR=3.923, p=0.009) and a higher annual frequency of outpatient visits (OR=1.125, p=0.004) were independent predictors of persistence. Cost-driver analysis revealed a polypharmacy paradox: while intensive care unit (ICU) admission significantly increased total costs, prescribing a higher number of distinct medication classes was independently associated with reduced cumulative total healthcare expenditure (β=-0.18159, p=0.00843). CMA confirmed that among patients with identical clinical outcomes, total healthcare costs did not differ significantly between persistent and non-persistent cohorts (p>0.05), indicating economic neutrality. Thirty-day medication persistence among Indonesian patients with CAD-related HF is low, but persistence represents a value-based, cost-neutral management strategy. Appropriate polypharmacy aligned with guideline-directed medical therapy may offset direct provider costs by preventing costly acute-care rehospitalizations.

Keywords: Cost-effectiveness; Heart failure; Medication persistence; Pharmacoeconomics; Polypharmacy

INTRODUCTION

Cardiovascular disease (CVD) is the principal cause of morbidity, mortality, and catastrophic healthcare expenditure globally, with heart failure (HF) serving as the terminal common pathway for various cardiac pathologies. In low- and middle-income countries (LMICs) such as Indonesia, rapid urbanization, epidemiological transitions, and a rising prevalence of metabolic risk factors, including hypertension and diabetes mellitus, have accelerated HF incidence (Nurhasanah & Yunus, 2025; Zakaria et al., 2022). Under the national universal health coverage scheme, Jaminan Kesehatan Nasional (JKN), administered by BPJS Kesehatan, cardiovascular care accounts for a disproportionate share of the national health budget. Despite standardized insurance benefits, patients and healthcare providers face substantial direct medical costs and secondary economic burdens due to frequent emergency room visits, prolonged inpatient stays, and intensive care utilization (Endarti et al., 2025; Fattah et al., 2023).

The post-discharge transition period represents a vulnerable window for patients hospitalized with acute

decompensated heart failure secondary to coronary artery disease (CAD). In Indonesia, 30-day readmission rates remain high, largely driven by suboptimal post-discharge care, poor self-management, complex comorbidities, and treatment non-persistence (Indriany et al., 2024). Medication persistence, defined as the duration from initiation to discontinuation of prescribed pharmacotherapy, is critical for achieving clinical stabilization, preventing ventricular remodeling, and reducing acute decompensation events. However, real-world medication persistence during the immediate post-discharge phase is often compromised by health literacy deficits, out-of-pocket travel costs, complex medication regimens, and fragmented outpatient refill systems (Salah et al., 2025).

A critical gap exists in real-world pharmacoeconomic evidence originating from local hospital administrative databases in Southeast Asia (Mlambo et al., 2024). Most published economic evaluations of HF therapy rely on decision-analytic models seeded with clinical trial data from high-income countries, which fail to capture local epidemiological characteristics, operational bottlenecks in health systems, and real-world hospital billing realities (T.-P.-L. Nguyen et al., 2023; Zakiyah et al., 2021). Furthermore, traditional pharmacoeconomic paradigms often regard multi-drug regimens solely as cost-accumulating burdens. Evidence evaluating independent drivers of hospital expenditure and the incremental cost-effectiveness of medication persistence within Indonesian tertiary care hospitals remains limited.

To address these gaps, this study evaluated the 30-day post-discharge medication persistence rate and its clinical and comorbidity predictors among patients with systolic HF and CAD at an Indonesian academic tertiary hospital. It also conducted a multidimensional pharmacoeconomic evaluation, incorporating Cost-Effectiveness Analysis (CEA), Cost-Minimization Analysis (CMA), and log-linear multivariate cost-driver regression to elucidate the relationships among treatment persistence, regimen complexity, clinical outcomes, and cumulative healthcare provider expenditures.

METHODS

Study Design and Setting

This observational retrospective cohort study was conducted using integrated electronic medical record (EMR) and administrative billing databases at UNS Hospital in Sukoharjo, Indonesia. The study protocol received formal approval from the Institutional Health Research Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret (Ethical Clearance No. 1.573/XII/HREC/2022). The ethics committee waived the requirement for informed consent for a fully anonymized secondary analysis of routine hospital administrative data.

Study Population and Selection Criteria

The target population comprised adult patients (≥18 years) diagnosed with systolic HF secondary to CAD who had their first index hospital admission between 2022 and 2023. The inclusion criteria required active enrollment in the JKN universal health insurance program, a primary discharge diagnosis of HF with concomitant CAD confirmed by clinical assessment and noninvasive cardiac imaging, and documented left ventricular systolic dysfunction (LVEF < 50%) on baseline transthoracic echocardiography. Patients were also required to have a discharge prescription containing at least one core guideline-directed heart failure medication class, such as Angiotensin-Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARBs), Beta-blockers (BB), Mineralocorticoid Receptor Antagonists (MRAs), or loop diuretics, along with complete administrative and clinical records covering index admission, outpatient visits, and prescription refill history over a 12-month follow-up horizon.

Patients were excluded if they presented with congenital heart disease or primary severe valvular heart disease. Additional exclusion criteria were end-stage renal disease (ESRD) requiring maintenance hemodialysis or peritoneal dialysis at baseline, as well as concurrent diagnoses of active malignancy, human immunodeficiency virus (HIV), active tuberculosis, or severe systemic autoimmune disease. The final study cohort comprised 284 patients who satisfied all eligibility criteria. A post hoc statistical power analysis confirmed that for continuous direct medical cost comparisons between persistent (n=39) and non-persistent (n=245) cohorts, assuming a medium effect size (Cohen's d=0.5) at a two-sided significance level of α=0.05, the sample size provided 80.2% statistical power to detect meaningful cost differences.

Operationalization of Medication Persistence

Medication persistence was operationalized according to the European Society for Patient Adherence, Compliance, and Persistence (ESPACOMP) Ascertaining Barriers for Compliance (ABC) taxonomy proposed by Vrijens et al. (2012). Persistence was defined as the continuous period from treatment initiation (hospital discharge) to treatment discontinuation. Operationally, a patient was classified as "Persistent" (Binary: Yes/No) if an official outpatient pharmacy prescription refill claim for at least one core HF medication class was recorded in the hospital integrated pharmacy database within days 25 to 35 post-discharge (±5-day grace window around the standard 30-day post-discharge refill interval). Patients without a refill claim within this window were categorized as "Non-Persistent".

Pharmacoeconomic and Cost Accounting Framework

The economic evaluation was conducted from the perspective of the healthcare provider (the hospital). Total healthcare cost was defined as the cumulative direct medical expenditure incurred per patient over the 12-month post-discharge follow-up period, extracted directly from verified hospital billing records. Direct medical costs encompassed index ward accommodation, Intensive Care Unit (ICU) stay expenditures, nursing care, laboratory and radiological diagnostic procedures, specialist consultation fees, medical consumables, and outpatient

pharmacotherapy. Indirect costs (e.g., productivity loss) and intangible costs were excluded. Costs were recorded in Indonesian Rupiah (IDR). Costs were not adjusted for inflation because of the short 24-month study window (2022–2023). For international comparison, IDR 15,500 is approximately USD 1.00.

Cost-effectiveness analysis (CEA) evaluated the incremental expenditure required per unit of clinical improvement. The Incremental Cost-Effectiveness Ratio (ICER) was calculated using Equation (1):

$$\text{ICER} = \frac{\text{Cost}_{\text{P}} - \text{Cost}_{\text{NP}}}{\text{Effect}_{\text{P}} - \text{Effect}_{\text{NP}}} = \frac{\Delta\text{Cost}}{\Delta\text{Effect}} \qquad (1)$$

where Cost and Effect are the group means of total direct cost and of the clinical effectiveness measure, respectively; P = persistent; NP = non-persistent.

Clinical effectiveness parameters evaluated included changes in left ventricular ejection fraction (ΔLVEF) and systolic blood pressure (ΔSBP), total length of hospital stay (LOS), 1-year rehospitalization frequency, and annual outpatient visit frequency. Negative ICER values were interpreted as economic dominance (i.e., persistence achieving superior clinical outcomes or regimen efficiency at lower net provider costs). Cost-Minimization Analysis (CMA) was conducted to compare direct healthcare costs between persistent and non-persistent groups within clinical outcome-matched subgroups. Methodologically, CMA is appropriate when clinical effectiveness does not differ significantly between groups ($p>0.05$). Non-parametric Wilcoxon rank-sum tests were used to evaluate cost neutrality across matched clinical subgroups.

Statistical Analysis

Data analysis was conducted using standard statistical software. Continuous variables were evaluated for normality using the Shapiro-Wilk test. Age was normally distributed and presented as Mean ± Standard Deviation (SD). All other continuous variables (LVEF, SBP, LOS, annual visits, total costs) exhibited skewed distributions and were reported as Median (Interquartile Range, IQR). Categorical variables were presented as absolute frequencies and percentages (n, %).

Bivariate comparisons between persistent and non-persistent cohorts were performed using Chi-square tests or Fisher's exact tests for categorical variables, and Wilcoxon rank-sum tests for continuous non-parametric variables. Independent predictors of 30-day medication persistence were identified by entering bivariate variables achieving $p<0.05$ into a multivariate logistic regression model. Results were expressed as Odds Ratios (OR) with 95% Confidence Intervals (CI).

Cost-driver analysis used a two-stage approach. Initial bivariate screening evaluated relationships between candidate patient factors and total direct costs using Wilcoxon rank-sum tests, Kruskal-Wallis tests, or Spearman rank correlation (ρ). Variables with significant associations ($p<0.05$) were entered into a multivariate linear regression model. To address skewness and heteroscedasticity inherent in cost data, total healthcare cost was natural-log-transformed (ln [Total Cost]) prior to regression modeling. Statistical significance was established at a two-tailed $p<0.05$.

RESULTS AND DISCUSSION

Baseline Clinical and Demographic Characteristics

The study evaluated 284 patients with systolic HF secondary to CAD. The cohort was predominantly male (81.3%, n=231) with a mean age of 59.3±10.3 years. Geriatric patients (≥60 years) comprised 25.0% (n=71) of the cohort. Most patients were married (90.5%, n=257) and had completed non-tertiary education (85.2%, n=242). Baseline median LVEF was 33.5% (IQR 14.0%), and baseline median SBP was 120.0 mmHg (IQR 30.0 mmHg).

Comorbidity screening demonstrated high rates of cardiovascular risk factors: history of hypertension was present in 58.1% (n=165), diabetes mellitus in 36.6% (n=104), prior myocardial infarction in 25.7% (n=73), active or former smoking in 57.4% (n=163), and documented kidney disease (non-dialysis chronic kidney disease) in 8.1% (n=23). Regarding index hospitalization, 66.6% (n=189) were treated in standard inpatient wards, while 33.4% (n=95) required intensive care (ICU) management. Rehospitalization within 12 months occurred in 43.3% (n=123) of patients. Overall baseline parameters are detailed in Table 1.

Table 1. Baseline Characteristics of Study Patients

Variable	Sub-category/Statistic	Value
Demographics		
Age	Mean ± SD	59.3 ± 10.3[a]
Gender	Male	231 (81.3%)[c]
	Female	53 (18.7%)[c]
Geriatric Category	Geriatric (≥60 years old)	71 (25.0%)[c]
	Non-Geriatric (<60 years old)	213 (75.0%)[c]
Marital Status	Married	257 (90.5%)[c]
	Not Married	27 (9.5%)[c]
Education	Non-Bachelor's	242 (85.2%)[c]
	Bachelor's	42 (14.8%)[c]
Clinical Status and Comorbidities		
Baseline Ejection Fraction (Pre-EF)	Median (IQR)	33.5% (14.0%)[b]
Post-treatment Ejection Fraction (Post-EF)	Median (IQR)	34.0% (15.0%)[b]
Baseline Systolic BP (Pre-Systolic BP)	Median (IQR)	120.0 mmHg (30.0)[b]
Post-treatment Systolic BP (Post-Systolic BP)	Median (IQR)	117.0 mmHg (24.0)[b]
Prior Myocardial Infarction	Present	73 (25.7%)[c]
	Absent/Unrecorded	211 (74.3%)[c]
Hypertension	History Present	165 (58.1%)[c]
	Absent/Unrecorded	119 (41.9%)[c]
Diabetes Mellitus (DM)	History Present	104 (36.6%)[c]
	Absent/Unrecorded	180 (63.4%)[c]
Chronic Kidney Disease (Non-dialysis)	History Present	23 (8.1%)[c]
	Absent/Unrecorded	261 (91.9%)[c]
Smoking History	Smoker (Active/Former)	163 (57.4%)[c]
	Non-Smoker	121 (42.6%)[c]

Variable	Sub-category/Statistic	Value
Treatment and Outcome		
Initial Renin-Angiotensin Therapy	ACE inhibitor	78 (27.5%)[c]
	ARB	161 (56.7%)[c]
	ACE inhibitor and ARB combination	45 (15.8%)[c]
Length of Index Hospital Stay (LOS)	Median (IQR)	5.0 days (4.25)[b]
1-Year Outpatient Visit Frequency	Median (IQR)	6.0 visits (10.0)[b]
Rehospitalization within 1 Year	Yes	123 (43.3%)[c]
	No	161 (56.7%)[c]
30-Day Medication Persistence	Persistent (Refill Day 25-35)	39 (13.7%)[c]
	Non-Persistent	245 (86.3%)[c]

Note: [a]Mean ± standard deviation (SD); [b]median (interquartile range [IQR]); [c]frequency (%).

Medication Persistence and Predictor Analysis

Only 13.7% (n=39) of patients satisfied the operational criteria for 30-day medication persistence. Bivariate analysis comparing persistent (n=39) and non-persistent (n=245) cohorts (Table 2) showed that demographic factors, including age, gender, educational level, and marital status, were not significantly associated with persistence (p>0.05). Similarly, baseline cardiac functional parameters, index admission length of stay, and baseline therapy class did not significantly differ between cohorts. Comorbidities were common, with a history of hypertension reported in 58.1% and diabetes mellitus (DM) in 36.6%. Most patients were treated in a standard inpatient ward (66.6%). Furthermore, 43.3% of patients experienced one or more rehospitalizations within a year, indicating a high overall disease burden.

Table 2. Bivariate Analysis of Factors Associated with Persistence at 30 Days

Variable	Category	Persistent (n=39)	Non-Persistent (n=245)	p-value
Demographics and Clinical				
Gender†	Male	32	199	1.000
	Female	7	46	
Age (years) ‡		58.0 (52.0-61.0)*	59.0 (53.0-66.0)*	0.263
Geriatric Category†	Geriatric	6	65	0.196
	Non-Geriatric	33	180	
Marital Status†	Married	36	221	0.903
	Unmarried	3	24	
Education†	Non-Graduate	35	207	0.538
	Graduate	4	38	
Hospitalization (Current) †	Yes	15	108	0.628
	No	24	137	
Admission Method†	Emergency	28	185	0.765
	Outpatient Clinic	11	60	
Referral†	Yes	18	82	0.174
	No	21	163	
Smoking†	Yes	18	145	0.176
	No	21	100	
Comorbidities				
Prior Myocardial Infarction†	History	12	61	0.702
	No History/Data	27	184	
Hypertension†	History	23	142	0.057
	No History/Data	16	103	
Diabetes Mellitus (DM)†	History	14	90	0.566
	No History/Data	25	155	
Stroke†	History	2	15	0.284
	No History/Data	37	230	
Kidney Disease†	History	7	16	0.015
	No History/Data	32	229	
Liver Disease†	History	0	12	0.340
	No History/Data	39	233	
Clinical Measures				
Length of Stay (days)‡		5.0 (2.5-7.5)*	5.0 (3.0-7.0)*	0.966
Baseline LVEF Category‡	<35%	23	129	0.574
	≥35%	16	116	
Mean LVEF (Pre-treatment)‡		33.19§	33.63§	0.797
Mean LVEF (Post-treatment)‡		33.31§	34.78§	0.386
Mean Systolic BP (Pre-treatment, mmHg)‡		127.4§	123.8§	0.381
Mean Systolic BP (Post-treatment, mmHg)‡		117.1§	118.3§	0.693
Post-Discharge History				
Frequency of Hospitalization‡		0.0 (0.0-1.0)*	0.0 (0.0-1.0)*	0.582
Annual Outpatient Visit Frequency‡		2.0 (2.0-4.0)*	7.0 (3.0-12.0)*	0.004
Rehospitalization at 30 Days‡		2.0 (2.0-2.0)*	2.0 (2.0-2.0)*	0.777
Treatment†				
Initial Therapy Class†	ACE Inhibitor	11	67	0.943
	ACE and ARB	1	8	
	ARB	21	140	
	Other	6	30	
Mean Number of Medication (Types)‡		2.85§	2.66§	0.371

Note: † Chi-squared test; ‡ t-test or Wilcoxon rank-sum test; * median (interquartile range); § mean.

Two parameters demonstrated statistically significant associations with 30-day persistence in bivariate testing: annual outpatient visit frequency (p=0.004) and a documented history of kidney disease (p=0.015). In the persistent cohort, 17.9% (n=7/39) had kidney disease compared to 6.5% (n=16/245) in the non-persistent cohort. In multivariate logistic regression (Table 3), both variables remained independent predictors of 30-day persistence: the absence of kidney disease and annual

outpatient visit frequency. Patients without chronic kidney disease had nearly fourfold higher odds of achieving 30-day medication persistence compared with those with renal comorbidity (OR=3.923, 95% CI: 1.417-10.863, p=0.009). In addition, each additional outpatient clinic visit over the follow-up year was associated with a 12.5% increase in the odds of achieving 30-day persistence (OR=1.125, 95% CI: 1.038-1.219, p=0.004).

Table 3. Logistic Regression Analysis

Predictor Variable	Regression Coefficient (β)	Std. Error (SE)	Odds Ratio	p-value
Model Intercept	0.048	0.529	-	0.928
Annual Outpatient Visit Frequency	0.118	0.041	1.125	0.004
No History of Kidney Disease (Ref: History Present)	1.367	0.520	3.923	0.009

Cost-Effectiveness Analysis (CEA)

CEA evaluated incremental financial commitments per unit of gain in intermediate clinical and utilization parameters (Table 4). The baseline incremental cost for persistent relative to non-persistent patients across standardized clinical measures was IDR 8,847,364.75. The ICER for achieving a 1% improvement in ejection fraction (ΔLVEF) was IDR 8,627,941.44 per unit gain (Δ Effect = 1.0254). The ICER for achieving a 1 mmHg reduction in systolic blood pressure (ΔSBP) was IDR 1,846,179.74 (Δ Effect = 4.7923). Two parameters showed negative incremental values. Pre-treatment systolic BP yielded a negative ICER (−IDR 2,477,407.33), reflecting lower overall costs relative to the baseline blood pressure burden. For the number of medication types, the persistent group had a negative incremental cost (Δ cost: −IDR 2,707,933.84; ICER = IDR 14,159,442.77), indicating that greater regimen persistence was associated with lower spending per drug class used. The full CEA/ICER results are detailed in Table 4.

Table 4. CEA/ICER Results for 30-Day Persistence

Clinical Effectiveness Endpoint	Incremental Cost (Δ Cost, IDR)	Incremental Effect (Δ Effect)	ICER (IDR per unit of effect)
Change in LVEF (ΔLVEF)	8,847,364.75	1.0254 %	8,627,941.44
Change in Systolic BP (ΔSBP)	8,847,364.75	4.7923 mmHg	1,846,179.74
Length of Stay (LOS)	8,847,364.75	1.4199 days	6,231,043.72
Hospitalization Frequency	8,847,364.75	0.1391 admissions	63,609,157.42
1-Year Outpatient Visit Frequency	8,847,364.75	2.4786 visits	3,569,504.29
Post-Treatment Cardiovascular Risk Score	10,141,796.92	14.383 points	705,124.93
Patient Age	8,847,364.75	2.1746 years	4,068,561.47
Baseline Ejection Fraction (Pre-EF)	8,847,364.75	0.4424 %	19,999,188.60
Post-Treatment Ejection Fraction (Post-EF)	8,847,364.75	1.4678 %	6,027,562.94
Baseline Systolic BP (Pre-SBP)	8,847,364.75	-3.5712 mmHg	-2,477,407.33
Post-Treatment Systolic BP (Post-SBP)	8,847,364.75	1.221 mmHg	7,245,784.71
Pre-Treatment Cardiovascular Risk Score	10,141,796.92	14.7617 points	687,034.38
Number of Medication Types	-2,707,933.84	-0.1912 classes	14,159,442.77

Cost-Minimization Analysis (CMA)

CMA evaluated whether direct healthcare costs differed significantly between persistent and non-persistent cohorts within clinical outcome-matched subgroups (Table 5). Direct healthcare costs did not differ significantly in any filtered subgroup (p>0.05), including surviving patients (mean cost difference of IDR 9,115,873; median persistent IDR 16,864,109 vs non-persistent IDR 29,240,857; p=0.1564), non-rehospitalized patients (mean cost difference of IDR 9,786,890; p=0.1405), intensive care cohort (mean cost difference of IDR 14,477,262; p=0.6846), and severe dysfunction with LVEF<35% (mean cost difference of -984,337 (p=0.7577). The consistent absence of significant differences across matched clinical endpoints supports economic neutrality, indicating that medication persistence delivers comparable clinical stability without imposing excess costs on the healthcare provider.

Identification of Independent Cost Drivers

Bivariate correlation and subgroup cost comparisons (Table 6) identified factors associated with total healthcare provider expenditures. Direct costs were significantly higher among patients requiring ICU admission (mean IDR 73,136,155 vs IDR 40,553,445 in standard wards; p<0.0001), those experiencing rehospitalizations (mean IDR 72,415,322 vs IDR 35,437,585 without rehospitalization; p<0.0001), smokers (p=0.02529), and referred patients (p=0.01862). Continuous metrics, including rehospitalization frequency (ρ=0.3117, p<0.0001), annual outpatient visit frequency (ρ=0.2836, p<0.0001), and pre-treatment LVEF (ρ=0.2160, p=0.00025), showed positive correlations with total costs. A negative correlation was observed between the number of prescribed medication classes and total healthcare expenditure (ρ = -0.1900, p = 0.00831), indicating that patients prescribed more medication classes tended to incur lower total costs.

Table 5. Cost-Minimization Analysis for 30-Day Persistence

Filtered Clinical Outcome Subgroup	Mean Cost Diff. (IDR)	Median Cost (Persistent) (IDR)	IQR (Persistent) (IDR)	Median Cost (Non-Persistent) (IDR)	IQR (Non-Persistent) (IDR)	p-value
Patient Survived	9,115,873	16,864,109	70,588,964	29,240,857	60,559,341	0.1564
No Rehospitalization	9,786,890	10,997,246	49,526,180	18,428,211	40,826,113	0.1405

Filtered Clinical Outcome Subgroup	Mean Cost Diff. (IDR)	Median Cost (Persistent) (IDR)	IQR (Persistent) (IDR)	Median Cost (Non-Persistent) (IDR)	IQR (Non-Persistent) (IDR)	p-value
Ward: Intensive Care	14,477,262	60,508,354	68,393,671	57,971,038	80,582,558	0.6846
Ward Class: Class 1 and VIP	4,563,684	19,889,499	86,822,052	36,888,423	58,327,027	0.5165
Geriatric Patient Category	10,145,825	21,423,189	44,841,492	33,989,723	48,318,000	0.7021
Active or Former Smoker	13,411,629	46,056,001	75,393,038	38,825,217	69,308,898	0.4896
Baseline LVEF <35%	-984,337	19,903,902	73,957,619	20,777,690	39,081,960	0.7577
Emergency Department Admission	11,088,434	19,889,499	64,678,131	31,939,621	62,708,575	0.1887

Table 6. Bivariate Analysis of Potential Cost Drivers

Candidate Variable	Sub-group/ Metric	Mean Direct Cost (IDR)	Median Direct Cost (IQR) (IDR)	Statistical Test/ Correlation	p-value
Gender	Male	54,132,031	31,968,549 (65,262,362)	Wilcoxon test	0.07686
	Female	39,774,275	19,837,325 (42,187,225)		
Ward Accommodation	Intensive Care Unit	73,136,155	58,055,718 (79,661,201)	Wilcoxon test	< 0.0001
	Standard Inpatient Ward	40,553,445	19,370,980 (40,323,417)		
Ward Class	Class 1 and VIP	58,511,876	34,494,168 (63,568,535)	Wilcoxon test	0.2568
	Classes 2 and 3	49,132,633	28,696,764 (61,059,508)		
Rehospitalization	Yes	72,415,322	47,778,829 (90,837,846)	Wilcoxon test	< 0.0001
	No	35,437,585	17,471,744 (43,201,043)		
Smoking History	Smoker	57,406,770	38,825,217 (71,041,935)	Wilcoxon test	0.02529
	Non-Smoker	43,431,671	19,121,666 (43,483,991)		
Referral Status	Referral	57,480,612	41,815,645 (74,672,577)	Wilcoxon test	0.01862
	Non-Referral	48,176,492	22,316,990 (50,912,462)		
Baseline EF Tier	LVEF<35%	44,105,213	20,763,009 (45,060,021)	Wilcoxon test	0.00295
	LVEF≥35%	59,913,207	42,700,033 (85,218,311)		
Hospitalization Frequency	Continuous	51,452,591	29,142,155 (61,346,230)	Spearman's ρ: 0.3117	< 0.0001
Annual Visit Frequency	Continuous	51,452,591	29,142,155 (61,346,230)	Spearman's ρ: 0.2836	< 0.0001
Baseline LVEF	Continuous	51,452,591	29,142,155 (61,346,230)	Spearman's ρ: 0.216	0.00025
Post-Treatment LVEF	Continuous	51,452,591	29,142,155 (61,346,230)	Spearman's ρ: 0.224	0.00014
Number of Meds	Continuous	51,452,591	29,142,155 (61,346,230)	Spearman's ρ: -0.19	0.00831

Multivariate log-linear regression modeling (Table 7) accounted for 37.3% of the total cost variance (adjusted R^2=0.373, F=15.42, p<0.001). The analysis identified four independent cost drivers, i.e., ward accommodation (initial treatment in standard inpatient wards (versus ICU) was associated with a significant reduction in natural log total expenditure (β=-0.84211, p<0.001)), absence of rehospitalization (avoiding hospital readmissions significantly reduced total provider costs (β=-0.50560, p=0.02205)), annual outpatient visit frequency (each additional outpatient visit was an independent driver of higher direct expenditures (β=0.06377, p<0.001)), and number of medication types ("polypharmacy paradox" or prescribing a higher number of distinct medication classes was independently associated with a statistically significant decrease in cumulative healthcare provider expenditures (β=-0.18159, p=0.00843).

Table 7. Multivariate Linear Regression for Cost Drivers

Independent Predictor Variable	Coefficient (β)	Standard Error (SE)	t-statistic	p-value
Regression Intercept	17.06642	0.49679	34.353	< 0.001
Ward Accommodation: Standard Ward (Ref: ICU)	-0.84211	0.17148	-4.911	< 0.001
No Rehospitalization (Ref: Rehospitalized)	-0.50560	0.21893	-2.309	0.02205
Rehospitalization Frequency	0.18925	0.09712	1.949	0.05289
Annual Outpatient Visit Frequency	0.06377	0.01587	4.020	< 0.001
Smoking Status: Non-Smoker	0.06017	0.15397	0.391	0.69641
Referral Status: Non-Referral	-0.15406	0.15989	-0.964	0.33658
Baseline Ejection Fraction Tier ≥35%	-0.07463	0.24422	-0.306	0.76028
Pre-Treatment Ejection Fraction (Pre-EF)	0.01802	0.01691	1.065	0.28818
Post-Treatment Ejection Fraction (Post-EF)	0.01060	0.01401	0.756	0.45047
Number of Medication Types	-0.18159	0.06817	-2.664	0.00843

Low Persistence Rates and Comparative Context

The global rise of cardiovascular disease (CVD) represents one of the most significant challenges to the fiscal stability of national healthcare systems, particularly in low- and middle-income countries (LMICs), where catastrophic conditions such as stroke and coronary heart disease consume approximately 13% of the national health insurance budget (Nurwahyuni et al., 2023). This study reveals a 30-day medication persistence rate of 13.7% among Indonesian CAD-HF patients following index

hospital discharge. This rate is not only suboptimal but also indicates a vulnerability in post-discharge transitional care within the national health system. Recent international literature consistently shows that persistence with single guideline-directed medical therapy (GDMT) components typically ranges from 31% (for mineralocorticoid receptor antagonists, or MRAs) to 58% (for beta-blockers or renin-angiotensin system inhibitors, or RASi), and even dual-therapy adherence is reported at 42% (Ødegaard et al., 2023). Furthermore, this rate lags behind GDMT adherence reported in other LMIC regions, such as India (28% receiving GDMT) and the Americas (21% on quadruple therapy) (Joseph et al., 2022; Sotomayor-Julio et al., 2025). This wide discrepancy suggests that the Indonesian cohort faces a critical confluence of patient- and system-level barriers that are uniquely magnified in resource-limited settings. The immediate post-discharge window, often termed the "vulnerable phase," is a critical period during which treatment discontinuation leads to early readmission. In Indonesia, where cardiovascular diseases account for a major portion of national health expenditures, early non-persistence exacerbates clinical instability and strains provider capacity (Nurwahyuni et al., 2023).

The Polypharmacy Paradox and Cost-Offset Mechanisms

The low persistence rate likely reflects deep-seated barriers that interact with the intensity of care. A key empirical finding of this evaluation is the "polypharmacy paradox," showing a counterintuitive, statistically significant negative correlation between the number of medication types and total costs (Nurwahyuni et al., 2023). While traditional healthcare management approaches often seek to reduce drug acquisition costs by minimizing the number of prescriptions (Joseph et al., 2022), the multivariate log-linear regression demonstrated that prescribing a higher number of distinct medication classes was independently associated with a statistically significant reduction in cumulative direct provider expenditure ($\beta = -0.18159$, $p = 0.00843$). This finding aligns with modern clinical trial evidence supporting early, comprehensive initiation of multi-agent GDMT, including quadruple therapy combining ACEi/ARBs/Angiotensin Receptor-Neprilysin Inhibitor (ARNI), evidence-based beta-blockers, MRAs, and Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors. Synergies achieved through multi-pathway neurohormonal blockade accelerate clinical stabilization, reduce the risk of acute decompensation, and prevent disease progression (Sotomayor-Julio et al., 2025).

In economic terms, aggressive multi-agent GDMT acts as a cost-offset mechanism: by promoting clinical stability, it keeps the cost of an additional daily pill small relative to the catastrophic expenditure of the events it prevents, particularly ICU admission, which was the strongest predictor of high total cost (A. B. Tang et al., 2025). The marginal expenditure of providing additional daily oral medications is small compared to the expenses associated with acute hospital readmissions (Mean: IDR 72,415,322) and intensive care unit accommodation (Mean: IDR 73,136,155). By preventing catastrophic utilization of acute care, comprehensive prescribing lowers cumulative hospital expenditures. Conversely, the regression model identified the frequency of annual outpatient visits as an independent driver of higher healthcare costs ($\beta = 0.06377$, $p < 0.001$). In non-persistent patients, frequent clinic visits reflect ongoing therapeutic instability, persistent symptoms, and repeated acute clinical contacts. Rather than serving as proactive preventive care, high visit frequency in non-persistent cohorts often signals sub-optimal disease control, leading to diagnostic re-evaluations and eventual inpatient re-admission (Achterbosch et al., 2025).

The Cardio-Renal Risk Phenotype and Clinical Predictors

The clinical high-risk phenotype is centered on the intersection of the cardiovascular and renal systems (Nurwahyuni et al., 2023). Multivariate logistic regression identified the absence of chronic kidney disease (OR=3.923, p=0.009) as the strongest independent predictor of 30-day medication persistence. This finding highlights the clinical challenges of managing cardio-renal syndrome. Moreover, this cohort faces unique challenges, including hyper-polypharmacy and logistical fatigue from managing non-cardiac drugs, increased risk of medication intolerance, and higher rates of psychological distress (depression or anxiety), which are known to reduce adherence (Laradhi et al., 2025; H.-Y. (Jean) Tang et al., 2014). Patients with combined cardiac and renal dysfunction face complex multi-drug regimens, complex dosing schedules, and heightened susceptibility to adverse drug reactions, hyperkalemia, or transient serum creatinine elevations following renin-angiotensin-aldosterone system (RAAS) inhibitor initiation (Tesfaye et al., 2020). Fearing progressive renal failure, clinicians or patients may prematurely discontinue core disease-modifying agents. This non-persistence in the cardio-renal group creates an economic multiplier, accelerating both ventricular failure and ESRD progression, which ultimately leads to the high cost of hemodialysis (Cedillo-Couvert et al., 2018; Zakiyah et al., 2021). Beyond this specific phenotype, the general barriers observed in LMICs are also highly relevant, such as low health literacy, forgetfulness, high out-of-pocket medication costs, drug stock-outs in rural facilities, and poor patient-provider communication, all of which fracture continuity of care (Harrison et al., 2023; Krishnamoorthy et al., 2022).

Economic Neutrality and Policy Implications

The CMA and CEA provide evidence to support value-based cardiovascular health policy in Indonesia. CMA demonstrated that across all outcome-matched clinical subgroups, including surviving patients, non-rehospitalized cohorts, and patients with severe systolic dysfunction, total direct expenditures did not differ significantly between persistent and non-persistent groups ($p>0.05$). This finding confirms economic neutrality, a phenomenon in which achieving treatment persistence does not increase net direct provider expenditure when controlling for

achieved clinical status. Furthermore, CEA demonstrated that persistent therapy achieved clinical stabilization with favorable ICERs (IDR 8,627,941.44 per 1% LVEF gain and IDR 1,846,179.74 per 1 mmHg SBP reduction) and exhibited economic dominance regarding treatment complexity costs. Over the 12-month horizon, persistence therefore behaved as a cost-neutral strategy. This finding is consistent with the projected cost savings of optimal adherence in other upper-middle-income economies, such as Thailand, China, and Mexico (Cho et al., 2024). A key strength of the Indonesian data is that the estimated savings are predominantly driven by direct healthcare cost avoidance, specifically through the reduction of high-cost events like hospitalization and ICU utilization, strengthening the economic case for hospital administrators and BPJS Kesehatan (Nurwahyuni et al., 2023; Ogungbe et al., 2021).

These economic and clinical findings suggest that clinicians and hospital administrators should adopt a precision-adherence management mindset rather than a mere prescribing mindset (Stolfo et al., 2025). Clinicians must recognize a history of kidney disease as a significant red flag, triggering a high-touch transition of care that involves early pharmacist follow-up (within 7 days) and multidisciplinary support to bridge the critical 30-day persistence gap (Craigo et al., 2025; H. N. Nguyen et al., 2023). The regression data support comprehensive prescribing of GDMT, with optimization as the goal, because spending more on prescriptions may prevent much larger spending on inpatient care (Nurwahyuni et al., 2023). Furthermore, the frequent-visit patient should not be viewed as a successful monitoring case but as a sign of therapeutic distress, prompting a comprehensive adherence review (Stolfo et al., 2025). Evidence strongly supports the implementation of multicomponent, pharmacist/nurse-led interventions and structured patient and caregiver education to overcome the pervasive barriers of low literacy and forgetfulness, so that investment in daily medication becomes an investment in the long-term sustainability of the national health system (Clements et al., 2023; Wang et al., 2024).

These findings support several health policy and clinical service adaptations within the Indonesian JKN framework. First, national health insurance reimbursement models, such as Indonesian case-based groups (INA-CBGs) and capitation, should evolve to financially reward providers for optimizing GDMT and achieving high adherence, thereby compensating them for the substantial cost avoidance generated for the central payer. Healthcare purchaser payment structures (such as INA-CBGs hospital reimbursement packages) should incentivize complete GDMT prescribing and 30-day post-discharge refill confirmation, recognizing that short-term pharmaceutical investments reduce downstream acute care claims (Chavarina et al., 2023). Secondly, strategic investment must be made in the high-risk ESRD population by funding targeted interventions for high-risk phenotypes. Specialized, multidisciplinary transition pathways that incorporate dedicated clinical pharmacists, early nurse-led post-discharge follow-up, and renal-cardiovascular co-management clinics should be established for high-risk cardio-renal patients to facilitate collaboration in medication reconciliation and counseling. The ICER data support the cost of these human resource interventions, which may prevent costly acute care (Disdier Moulder et al., 2020). Finally, to address the logistical burden of polypharmacy, policy should favor the inclusion of fixed-dose combinations (FDCs) in the national formulary. FDCs could reduce pill burden, simplify refill logistics, and improve treatment persistence (Kohli-Lynch et al., 2025).

Study Limitation

Several methodological limitations should be considered when interpreting these findings. First, the observational retrospective cohort design used administrative medical and billing records, making the findings susceptible to unmeasured confounding and recording errors. Thus, causal inference cannot be established. Second, selection and behavioral bias, particularly the "healthy adherer effect" whereby persistent patients also tend to adopt healthier behaviors (e.g., dietary sodium restriction, smoking cessation, symptom self-monitoring), cannot be fully isolated in retrospective administrative databases. Third, data were collected from a single academic tertiary hospital in Central Java, which may limit generalizability to secondary regional facilities or non-academic community centers across Indonesia. Fourth, medication persistence was assessed at the 30-day post-discharge mark using hospital pharmacy refill claims. This timeframe is too short to capture the long-term adherence challenges of chronic disease management. Moreover, out-of-pocket fills at external commercial pharmacies were not recorded, and long-term, multi-year persistence patterns were not evaluated. Finally, health-related quality of life (HRQoL) utilities and QALYs could not be calculated due to the lack of preference-based patient questionnaires in routine administrative records.

CONCLUSIONS

In this Indonesian cohort of patients with systolic HF secondary to CAD, 30-day post-discharge medication persistence was low (13.7%). Multivariate analysis identified kidney disease as a strong independent barrier to persistence, whereas higher outpatient visit frequency was associated with greater persistence. Pharmacoeconomic evaluation demonstrated the "polypharmacy paradox," showing that prescribing more GDMT classes was independently associated with lower total direct healthcare provider expenditure, possibly by preventing costly rehospitalizations and intensive care stays. Furthermore, cost-minimization analysis confirmed that 30-day medication persistence is economically neutral across matched clinical outcomes.

SUGGESTION

This study suggests that avoided acute care services may offset the upfront investment in chronic

pharmacotherapy. Clinically, the strongest predictors of non-persistence were renal comorbidity and lower outpatient visit frequency. Therefore, health policy and clinical practice should prioritize the structured optimization of multi-agent GDMT, implement targeted transitional care programs for high-risk cardio-renal patients, and adopt value-based reimbursement frameworks under the national health insurance scheme to support long-term medication persistence and health system sustainability.

DECLARATIONS AND ETHICAL STATEMENTS

Ethical Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and formally approved by the Institutional Health Research Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret (Certificate of Ethical Clearance No. 1.573/XII/HREC/2022). Patient consent was waived due to the retrospective, non-interventional design utilizing anonymized secondary administrative records.

Conflict of Interest Disclosures

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Artificial Intelligence (AI) Usage Statement

The authors used Claude (Anthropic, San Francisco, CA, USA) to refine phrasing and linguistic nuance in the English-language presentation of this manuscript. All intellectual content, arguments, and conclusions are the authors' own. The authors take full responsibility for the integrity of the published work.

Author Contributions

Ratih Puspita Febrinasari conceptualized the study, led the study design, performed primary data analysis, and drafted the manuscript. Benedictus and Stefanus Erdana Putra managed database extraction, statistical modeling, and pharmacoeconomic calculations. Christopher William Purnomo and Tivano Antoni conducted the literature review and clinical data extraction. Nurhasan Agung Prabowo provided clinical supervision, validated the interpretation of the data, and critically revised the manuscript for scientific content. All authors reviewed, refined, and approved the final manuscript version prior to submission.

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