

# Excessive Polypharmacy Among Indonesian Heart Failure Patients: Clinical Correlates and Care Implications

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## Abstract

**Background:** Heart Failure (HF) is a major global health problem that often coexists with multiple chronic comorbidities, requiring complex pharmacotherapy. The use of numerous concurrent medications increases the risk of polypharmacy and excessive polypharmacy, which may lead to adverse drug reactions, drug–drug interactions, poor adherence, and higher healthcare utilization. Despite growing awareness of this issue, evidence on the prevalence and determinants of excessive polypharmacy among Indonesian HF patients remains scarce.

**Methods:** This single-center cross-sectional sub-analysis was derived from a cross-sectional study involving 494 adult HF patients treated at Hasna Medika Cardiovascular Hospital, Cirebon, between January and December 2023. HF diagnosis was confirmed by cardiologists using the European Society of Cardiology (ESC) criteria. Polypharmacy was defined as the use of  $\geq 7$  medications, while excessive polypharmacy was defined as  $\geq 10$  medications. Clinical and demographic variables were extracted from Electronic Medical Records (EMR). Bivariate analysis was performed using Chi-square or Fisher's exact tests, followed by multivariate logistic regression to identify independent determinants of excessive polypharmacy.

**Results:** The mean age of participants was  $58.1 \pm 10.5$  years, and 53.4% were male. Overall, 42.5% of patients met the criteria for polypharmacy, and 15.6% ( $n=77$ ) met the criteria for excessive polypharmacy. The most frequent comorbidities were Coronary Artery Disease (CAD) (80.2%), hypertension (23.1%), and Type 2 Diabetes Mellitus (T2DM, 20.0%). In multivariate analysis, T2DM (Adjusted Odds Ratio [AOR] 17.21, 95% CI 8.39–35.34), Chronic Kidney Disease (CKD) (AOR 5.97, 95% CI 2.37–15.03), Chronic Obstructive Pulmonary Disease (COPD) (AOR 6.64, 95% CI 2.64–16.69), and asthma (AOR 26.32, 95% CI 5.79–119.67) were identified as independent determinants of excessive polypharmacy. The model demonstrated good fit (McFadden pseudo- $R^2 = 0.351$ ; Hosmer–Lemeshow  $p = 0.62$ ).

**Conclusions:** Excessive medication burden is common among HF patients, particularly among those with metabolic and pulmonary comorbidities. These findings highlight the need for systematic medication review and rational prescribing strategies while recognizing that higher medication counts do not necessarily indicate inappropriate prescribing.

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## Introduction

Heart Failure (HF) is a severe, progressive condition where the heart struggles to pump enough blood to meet the body's demands for oxygen and nutrients. It represents the advanced stage of various heart conditions, such as Coronary Artery Disease (CAD), high blood pressure, and cardiomyopathies. HF is a growing global health concern, impacting an estimated 64 million people worldwide, and its incidence and prevalence are rising despite medical advancements.<sup>1-5</sup> This disease creates significant economic and healthcare challenges due to frequent hospitalizations, lost productivity, and high long-term care expenses. In many regions, HF accounts for 1-2% of total healthcare spending, highlighting its substantial impact on patients and health systems.

Globally, HF affects 1-2% of adults, with prevalence sharply increasing to over 10% in individuals over 70. In Asia, recent data indicate an Age-Standardized Prevalence Rate (ASR) of roughly 722.5 per 100,000 people, with Southeast Asian nations showing a consistent upward trend.<sup>2-3</sup> The situation in Indonesia is particularly worrying, with an estimated ASR of 900.9 per 100,000, which is considerably higher than in many neighboring Southeast Asian countries.<sup>6</sup> Additionally, Indonesia reports higher one-year mortality rates, suggesting issues with disease recognition, limited access to effective treatments, and inconsistent application of clinical guidelines. These findings emphasize the urgent need to enhance HF management strategies in Indonesia through improved diagnosis, standardized treatment, and integrated chronic care. Effective HF treatment involves a comprehensive approach that combines medications, lifestyle changes, and device-based therapies. For patients with Heart Failure with reduced Ejection Fraction (HFrEF), the “four pillars of therapy”— $\beta$ -blockers, Angiotensin-Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARBs) (or Angiotensin Receptor–Neprilysin Inhibitor [ARNIs]), Mineralocorticoid Receptor Antagonists (MRA), and Sodium–Glucose Cotransporter 2 (SGLT2) inhibitors—are proven to decrease both illness and death.<sup>7</sup> However, HF rarely occurs in isolation. It is common for patients

to have multiple chronic conditions, such as Type 2 Diabetes Mellitus (T2DM), Chronic Kidney Disease (CKD), Chronic Obstructive Pulmonary Disease (COPD), hypertension, and Atrial Fibrillation (AF).<sup>8-9</sup>

Each of these co-existing conditions requires specific medications, leading to polypharmacy, which is the concurrent use of multiple drugs. The role of polypharmacy in HF is intricate. On the one hand, using multiple medications may be appropriate, reflecting guideline-directed medical therapy targeting distinct disease mechanisms. On the other hand, excessive or poorly coordinated polypharmacy increases risks such as adverse drug reactions, drug–drug and drug–disease interactions, poor adherence, and redundant therapies.<sup>10-12</sup> The threshold for defining polypharmacy varies considerably across studies. While the use of  $\geq 5$  medications is commonly adopted in general populations, this threshold may overestimate inappropriate medication burden in HF populations because guideline-directed medical therapy alone frequently requires multiple concurrent agents. Therefore, thresholds of  $\geq 7$  medications for polypharmacy and  $\geq 10$  medications for excessive polypharmacy were prespecified based on previous HF-specific and multimorbidity literature, aiming to better distinguish expected therapeutic complexity from excessive medication burden. Given the high prevalence of multiple comorbidities in HF, distinguishing between necessary and excessive medication use is vital for improving patient outcomes.

International registry data, including those from the ESC-HF Long-Term Registry, CHAMP-HF, and Asian-HF Registry, have shown high rates of polypharmacy among HF patients, especially those with cardio–renal–metabolic comorbidities.<sup>13</sup> However, data from Indonesia are scarce, with no previous studies comprehensively detailing the extent, composition, and factors contributing to excessive polypharmacy in local HF populations. This knowledge gap hinders clinicians and policymakers from implementing rational prescribing and deprescribing strategies tailored to the Indonesian healthcare system.

Against this backdrop, the Cirebon Heart Failure Cohort offers a unique opportunity to examine real-world medication patterns and quantify the burden of polypharmacy in a representative Indonesian population.<sup>14</sup> This sub-analysis, utilizing detailed Electronic Medical Record (EMR) data from a tertiary cardiovascular referral center, aims to identify clinical factors and comorbidities linked to excessive polypharmacy ( $\geq 10$  medications) among HF patients.

## Methods

### Study Design

This study is a sub-analysis of a cross-sectional observational study conducted at Hasna Medika Cardiovascular Hospital, a tertiary referral center specializing in cardiovascular diseases in Cirebon, West Java, Indonesia. The hospital serves both urban and peri-urban populations across the Cirebon region, providing a representative overview of real-world HF management in a mixed healthcare setting. Data were obtained from the hospital's EMR system, which comprehensively documents patient demographics, clinical diagnoses, echocardiographic parameters, comorbidities, and medication prescriptions. Data collection covered all outpatient visits between January 1 and December 31, 2023, ensuring a complete annual representation of HF cases managed in the tertiary outpatient setting. The previous study aimed to describe the demographic, clinical, and pharmacologic characteristics of HF patients in Cirebon, while this sub-analysis specifically focused on evaluating the determinants of excessive polypharmacy among these patients.

### Study Population and Sampling

The study population included all adult patients aged  $\geq 18$  years with a confirmed diagnosis of HF, as established by treating cardiologists based on clinical presentation, diagnostic work-up, and echocardiographic findings consistent with the European Society of Cardiology (ESC) guidelines for HF diagnosis. Only patients with complete clinical and medication documentation were eligible. A total sampling method was used to include all eligible patients who met the inclusion criteria during the study period. Patients were excluded if medication records were incomplete or unclear, if they were hospitalized or undergoing acute treatment at the time of data abstraction, or if the HF diagnosis could not be confirmed by

echocardiographic criteria. After applying these criteria, a final sample of 494 patients was included for analysis. This sample size was deemed adequate to provide sufficient statistical power to detect associations between comorbidities and excessive polypharmacy, based on logistic regression analysis.

### Study Definitions

HF subtypes were categorized based on Left Ventricular Ejection Fraction (LVEF) as follows: HF<sub>r</sub>EF with LVEF  $\leq 40\%$ , HF<sub>mr</sub>EF (Heart Failure with Mildly Reduced Ejection Fraction) with LVEF 41–49%, and HF<sub>p</sub>EF (Heart Failure with Preserved Ejection Fraction) with LVEF  $\geq 50\%$ .<sup>11</sup> Polypharmacy was defined as the concurrent use of  $\geq 7$  medications, while excessive polypharmacy referred to  $\geq 10$  medications. These thresholds were prespecified prior to analysis based on previous literature evaluating medication burden in HF populations where standard guideline-directed therapy frequently requires multiple concurrent medications.<sup>10</sup>

Comorbidities were defined as physician-documented chronic medical conditions recorded in the EMR. These included, but were not limited to, CAD, T2DM, CKD, COPD, asthma, hypertension, dyslipidemia, AF, cerebrovascular disease, and Chronic Venous Insufficiency (CVI). Prescribed drugs were grouped into pharmacological classes according to the Anatomical Therapeutic Chemical (ATC) classification system (e.g., beta-blockers, ACEi/ARB/ARNI, MRAs, loop diuretics, antiplatelets, antihyperglycemics, and respiratory agents). Fixed-dose combinations were counted as a single medication when prescribed as a single formulation.

### Data Management and Quality Control

Data extraction was performed by two trained research assistants under the supervision of the principal investigator (YPR). Random checks and cross-validation of 10% of entries were conducted to ensure accuracy and consistency. Incomplete or inconsistent entries were verified against original patient charts before final inclusion. To maintain data integrity, double-entry verification was applied during database creation.

### Statistical Analysis

Data were analyzed using Stata version 17.0. Continuous variables were summarized as means  $\pm$  Standard Deviations (SD) for normally distributed data, or as medians with Interquartile Ranges (IQR) for skewed distributions. Categorical variables were presented as frequencies and percentages. Associations between excessive polypharmacy

(dependent variable) and independent variables (age, sex, comorbidities, and Ejection Fraction [EF] category) were first explored using the Chi-square test or Fisher's exact test, as appropriate. Variables were initially screened using bivariate analyses. Variables with p-values <0.25, together with clinically relevant variables identified a priori (including age, sex, HF phenotype, CAD, hypertension, AF, Percutaneous Coronary Intervention (PCI) history, and comorbidity burden), were considered during multivariable model construction. Final covariate selection was based on clinical relevance, model stability, and avoidance of multicollinearity.

A multivariate logistic regression model was used to identify independent determinants of excessive polypharmacy ( $\geq 10$  drugs). Results were reported as Adjusted Odds Ratios (AORs) with 95% confidence intervals (CIs). Model fit was assessed using McFadden's pseudo- $R^2$  and the Akaike Information Criterion (AIC). The Hosmer–Lemeshow goodness-of-fit test was applied to evaluate model calibration. Statistical significance was defined as  $p < 0.05$  (two-tailed). All analyses were designed to identify clinically meaningful determinants of excessive medication use and to support the development of rational prescribing strategies in the HF population.

### Ethical Approval

Ethical approval was obtained from the Research Ethics Committee of Gunung Jati General Hospital (No. 060/LAIKETIK/KEPPKRSGJ/X/2024). All patient data were anonymized.

## Results

A total of 494 patients with clinically confirmed HF were included in the analysis. The mean age of the cohort was  $58.1 \pm 10.5$  years (range 27–86 years), and 53.4% ( $n = 264$ ) were male. Age distribution showed that almost half of the sample were middle-aged adults (45–59 years, 46.0%), while 40.1% were aged 60–74 years; patients aged  $\geq 75$  years represented 5.1% of the population. LVEF categories were relatively evenly represented: 35.0% had HFrEF, 31.8% had HFmrEF, and 33.2% had HFpEF (Table 1). Comorbid conditions were common and contributed substantially to treatment complexity. CAD was present in 80.2% of patients, hypertension in 23.1%, and T2DM in 20.0%. Less frequent but clinically relevant comorbidities included CKD (7.7%), COPD (8.9%), AF (14.4%), CVI (7.3%), stroke (2.2%), asthma (2.0%), and dyslipidemia (2.8%). Overall, 171 patients (34.6%) had three or more documented comorbidities, indicating a substantial burden of multimorbidity within this tertiary referral population (Figure 1).

The mean number of prescribed medications per patient was  $6.82 \pm 2.66$  (range 2–16), with a modal value of five drugs. When applying prespecified thresholds, 42.5% of patients ( $n = 210$ ) met the study definition of polypharmacy ( $\geq 7$  drugs), and 15.6% of the total cohort ( $n = 77$ ) met criteria for excessive polypharmacy ( $\geq 10$  drugs). Among patients meeting the excessive polypharmacy definition, the median number of drugs was 11 (IQR 10–13), highlighting

**Table 1.** Baseline characteristics of heart failure patients ( $n=494$ ).

Sample Characteristic	n	%
Sex		
Male	264	53.4
Female	230	46.6
Age group (mean age $\pm$ SD)	$58.1 \pm 10.48$	
18–44	44	8.9
45–59	227	46.0
60–74	198	40.1
$\geq 75$	25	5.1
Number of medications (mean $\pm$ SD)	$6.82 \pm 2.66$	
$\leq 4$ drugs	75	15.2
5 drugs	115	23.3
6 drugs	94	19.0
$\geq 7$ drugs (polypharmacy)	210	42.5
Comorbidities		
$< 3$	323	65.5
$\geq 3$	171	34.6

HF Classification		
HFrEF ( $\leq 40\%$ )	173	35.0
HFmrEF (41–49%)	157	31.8
HFpEF ( $\geq 50\%$ )	164	33.2
History of PCI (yes)	103	20.9

HF: Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; PCI: Percutaneous Coronary Intervention.

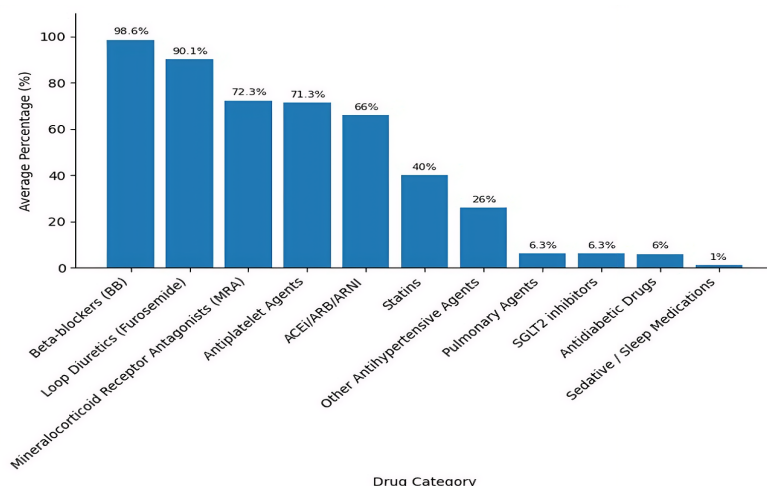


Figure 1. Proportion of prescribed medication classes among heart failure patients (n=494).

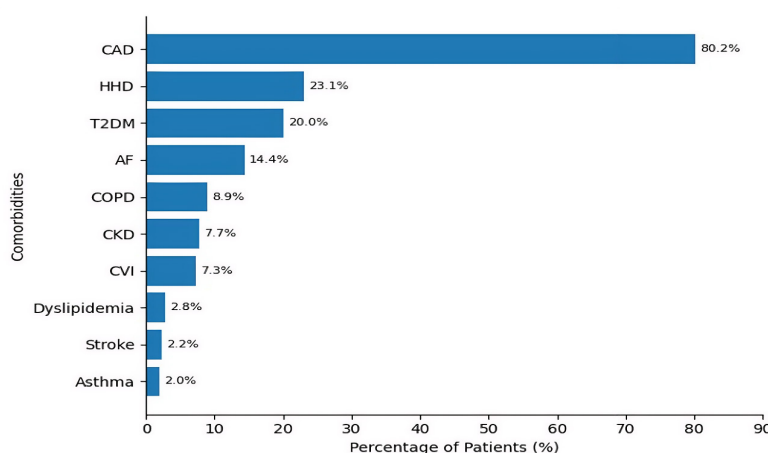


Figure 2. Distribution of comorbidities among heart failure patients (n=494).

a subgroup exposed to very high treatment intensity. Distribution by discrete medication counts showed 15.2% of patients received  $\leq 4$  drugs, 23.3% received 5 drugs, and 19.0% received 6 drugs, reinforcing that the medication burden was concentrated in a substantial minority of patients.

Analysis of drug classes revealed that guideline-directed HF therapies were commonly prescribed: beta-blockers were used by 98.6% of patients, loop diuretics (predominantly furosemide) by 90.1%, and mineralocorticoid receptor antagonists by 72.3%. Aspirin or other antiplatelet agents were used in 71.3%, and ACEi/ARBs/ARNIs in 66.0%

of patients (Figure 2). Despite strong evidence for their benefit in contemporary HF care, SGLT2 inhibitors were prescribed to only 6.3% of patients, indicating limited uptake in this setting. Among patients with diabetes, metformin (4.1% of the entire cohort) and glimepiride (3.9%) were the most frequently recorded antihyperglycemic agents. Respiratory therapies were less prevalent overall but concentrated among those with pulmonary comorbidity; salbutamol inhalation was recorded in 4.3% and ipratropium bromide in 2.8% of the cohort.

Univariate comparisons demonstrated that age 45–59 years, having  $\geq 3$  comorbidities, T2DM, CAD, CKD, COPD, asthma, and prior PCI were significantly associated with polypharmacy ( $p < 0.05$  for each). There was no statistically significant association between polypharmacy and sex or EF category in bivariate testing (sex  $p = 0.48$ ; EF category  $p = 0.21$ ). Given these findings, variables with  $p < 0.25$  in bivariate screening were entered into multivariate logistic regression to identify independent determinants of excessive polypharmacy ( $\geq 10$  drugs).

In multivariate logistic regression analysis, four comorbid conditions emerged as strong independent predictors of excessive polypharmacy. T2DM was associated with the greatest adjusted odds (AOR 17.21, 95% CI 8.39–35.34;  $p < 0.001$ ), indicating that diabetic patients were markedly more likely to receive 10 or more medications compared

with non-diabetic patients. CKD was independently associated with excessive polypharmacy with an AOR of 5.97 (95% CI 2.37–15.03;  $p < 0.001$ ). Pulmonary comorbidities also had large effect sizes: COPD (AOR 6.64; 95% CI 2.64–16.69;  $p < 0.001$ ) and asthma (AOR 26.32; 95% CI 5.79–119.67;  $p < 0.001$ ) were both strongly associated with excessive medication burden (Table 2). Although patients with  $\geq 3$  comorbidities showed a directionally increased odds of excessive polypharmacy (AOR 1.90), this association did not reach conventional statistical significance (95% CI 0.96–3.77;  $p = 0.067$ ), suggesting that the type of comorbidity is a more powerful driver of medication burden than comorbidity count alone. However, the large effect estimates and wide confidence intervals, particularly for asthma, should be interpreted cautiously because relatively small subgroup sizes may introduce sparse-data effects and model instability.

**Table 2.** Determinants of excessive polypharmacy (Multivariate logistic regression analysis).

Variable	AOR	95% CI	p-value
T2DM	17.21	8.39 – 35.34	<0.001
CKD	5.97	2.37 – 15.03	<0.001
COPD	6.64	2.64 – 16.69	<0.001
Asthma	26.32	5.79 – 119.67	<0.001
$\geq 3$ Comorbidities	1.90	0.96 – 3.77	0.067

AOR: Adjusted Odds Ratio; CI: Confidence Interval T2DM: Type 2 Diabetes Mellitus; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease.

**Table 3.** Fit model test.

Analysis	Value
McFadden's pseudo-R <sup>2</sup>	0.351
AIC	289.53
Hosmer–Lemeshow	0.62

AIC: Akaike Information Criteria.

The model exhibited good explanatory capacity and adequate calibration. McFadden's pseudo-R<sup>2</sup> was 0.351, indicating that the included predictors accounted for a substantial proportion of the variance in excessive polypharmacy. The AIC for the model was 289.53, and the Hosmer–Lemeshow goodness-of-fit test indicated satisfactory calibration ( $p = 0.62$ ) (Table 3). Mean medication counts differed markedly across clinically relevant subgroups. Patients with T2DM had a mean medication count of  $10.9 \pm 2.7$  compared with  $6.1 \pm 2.3$  among non-diabetic patients ( $p < 0.001$ ). Those with CKD had a mean of  $9.4 \pm 3.1$  drugs, and patients with COPD or asthma averaged  $10.7 \pm 2.8$  drugs. When patients were dichotomized by comorbidity burden, those

with  $\geq 3$  comorbidities received a mean of  $9.5 \pm 2.8$  medications, compared with  $5.3 \pm 1.9$  in those with fewer than 3 comorbidities ( $p < 0.001$ ). These descriptive comparisons reinforce the multivariable findings that cardio–renal–metabolic and pulmonary conditions are associated with substantially greater medication exposure.

## Discussion

This sub-analysis reveals that excessive polypharmacy is highly common among HF patients in Indonesian tertiary care settings, particularly those with co-occurring conditions like T2DM, CKD, COPD, and asthma. These results highlight

that the type and pathophysiological nature of comorbidities, rather than simply their number, are the primary factors driving the medication burden. This observation aligns with international registry data showing the significant role of the cardio-renal-metabolic axis in shaping the complexity of HF pharmacotherapy. The presence of multiple chronic diseases necessitates overlapping, often interacting treatments aimed at metabolic control, renal protection, and cardiovascular prevention.<sup>15</sup>

The notably high AOR for T2DM found in this study likely reflects the combined impact of multi-drug regimens that include both glucose-lowering and cardioprotective agents. HF patients with diabetes often require combinations of medications, including metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, and, increasingly, SGLT2 inhibitors, in addition to the four fundamental HF drugs (beta-blockers, ACEi/ARB/ARNI, MRAs, SGLT2 inhibitors). These overlapping treatment areas increase the number of medications and raise the risk of drug-drug interactions and adherence challenges. The relatively low utilization of SGLT2 inhibitors despite their established benefits across the cardio-renal-metabolic continuum likely reflects ongoing barriers, including cost, availability, reimbursement limitations, and delayed implementation within routine practice. Previous studies, including the CHAMP-HF registry and the QUALIFY study, similarly reported that diabetic HF patients receive significantly more prescriptions than non-diabetic patients, primarily due to cardiometabolic overlap.<sup>16</sup>

In patients with CKD, excessive polypharmacy is partly explained by the need for additional medications to correct electrolyte imbalances, manage uremic symptoms, and prevent anemia progression. Drugs such as phosphate binders, potassium regulators, erythropoiesis-stimulating agents, and bicarbonate supplements are frequently co-prescribed. However, CKD also restricts the use or dosage adjustment of crucial HF drugs like ACEi/ARBs, MRAs, and ARNIs due to the risk of hyperkalemia and worsening renal function. This dual therapeutic challenge—requiring more drugs while limiting standard HF therapies—is a defining characteristic of the cardio-renal syndrome, a concept gaining recognition in both European and Asian HF populations.<sup>17</sup> The intricate balance between therapeutic effectiveness and renal safety significantly contributes to the excessive polypharmacy observed in this patient group.

Pulmonary comorbidities like COPD and asthma further exacerbate the pharmacological burden. Their co-occurrence with HF is frequent, given shared risk factors such as smoking, aging, and systemic inflammation. Management typically involves multiple inhaled bronchodilators ( $\beta_2$ -agonists, antimuscarinics), inhaled corticosteroids, and sometimes systemic corticosteroids or antibiotics for exacerbations. These medications can interact unfavorably with HF treatments— $\beta$ -agonists can worsen tachycardia and arrhythmias, corticosteroids may cause fluid retention and aggravate HF symptoms, and certain antibiotics (e.g, macrolides) can prolong QT intervals.<sup>18</sup> This interaction creates a therapeutic dilemma that calls for individualized and multidisciplinary management, ideally involving cardiologists, pulmonologists, and pharmacists.

Within the Indonesian healthcare context, structural and systemic factors likely heighten the risk of excessive polypharmacy. Fragmented care delivery between hospitals and primary care, limited medication formularies, and inconsistent adherence to evidence-based guidelines contribute to overlapping or redundant prescriptions. For instance, the low adoption of SGLT2 inhibitors and ARNIs in Indonesia—despite their proven benefits in both HFrEF and HFpEF—points to ongoing challenges in accessibility, cost, and clinician familiarity.<sup>19</sup> Addressing these obstacles requires not only education and system integration but also policy reforms to include newer, guideline-directed medical therapies in national formularies and insurance coverage. Disease severity may substantially influence medication burden in HF populations. Variables such as New York Heart Association (NYHA) functional class, duration of HF, history of hospitalization, severity of renal function, natriuretic peptide levels, and continuous LVEF measurements may influence prescribing intensity and medication burden. Unfortunately, these variables were not fully available in the EMR system and therefore could not be analyzed.

An additional finding worth highlighting is the relatively lower utilization of ACEi/ARB/ARNI compared with beta-blockers and MRAs. Several explanations may contribute to this pattern. First, the presence of CKD and concerns regarding worsening renal function or hyperkalemia may limit prescription or dose optimization of renin-angiotensin system inhibitors.<sup>20</sup> Second, financial barriers and limited formulary availability may restrict access to newer agents such as ARNIs in routine clinical practice. Finally, real-world prescribing

inertia and physician preference may contribute to differential adoption of guideline-directed therapies within resource-limited healthcare systems.

Furthermore, this study reinforces the concept of the cardio-renal-metabolic continuum, which acknowledges the interconnected pathophysiology of heart, kidney, and metabolic disorders.<sup>21-22</sup> The emergence of SGLT2 inhibitors as a class of drugs with diverse benefits—improving cardiovascular outcomes, reducing HF hospitalization, and slowing CKD progression—represents a significant shift from symptom management to disease modification.<sup>23-24</sup> However, incorporating these therapies into already complex regimens demands precision and careful monitoring to prevent therapeutic duplication or unnecessary polypharmacy. Therefore, the rationalization of pharmacotherapy should aim to maximize disease-modifying drugs while minimizing redundant symptomatic agents.<sup>25-29</sup>

The international perspective offers valuable context. The ESC-HF-LT registry, CHAMP-HF registry, and Japanese CHART-2 cohort all reported average medication counts of 9-12 among HF patients with multiple comorbidities.<sup>29-31</sup> Our findings align with these trends, indicating that the burden of polypharmacy in HF is a universal issue, irrespective of the healthcare system. Nevertheless, in low- and middle-income countries like Indonesia, the consequences might be more severe due to limited resources, varying medication adherence, and limited integration of pharmacists into outpatient care.<sup>32</sup>

### Strengths and Limitations

This study has several notable strengths. It is one of the first investigations in Indonesia to systematically quantify the prevalence and determinants of excessive polypharmacy among HF patients using a clinically verified cohort with comprehensive medication documentation. The use of real-world data extracted from EMR enhances the validity and applicability of the findings to current clinical practice. Furthermore, the application of multivariate logistic regression analysis provides robust identification of independent predictors of excessive polypharmacy, minimizing confounding effects from demographic and comorbidity-related variables.

Nevertheless, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference regarding the temporal relationship between comorbidities and the development of excessive polypharmacy. Future

longitudinal or prospective studies are needed to determine whether polypharmacy directly contributes to adverse clinical outcomes, such as hospitalization, medication non-adherence, or mortality. Second, this study was conducted at a tertiary cardiovascular referral center; the patient population was predominantly composed of individuals with CAD and complex cardiovascular conditions. Therefore, referral bias may exist, and the medication burden observed in this cohort may not fully represent community-based or primary care HF populations. Despite these limitations, the study provides an essential early framework for understanding the multidimensional determinants of excessive polypharmacy in HF within an Indonesian healthcare context. It establishes a basis for future multicenter, longitudinal, and interventional studies aimed at evaluating deprescribing strategies, clinical outcomes, and the cost-effectiveness of integrated polypharmacy management programs.

## Conclusion

Excessive polypharmacy is highly prevalent among HF patients in Indonesia, especially in those with comorbidities such as T2DM, CKD, COPD, and asthma. These findings highlight that medication burden in HF is driven not merely by the number of coexisting conditions, but by the complexity and interdependence of cardio-renal-metabolic and pulmonary comorbidities. The coexistence of these systemic disorders results in overlapping pharmacological domains, leading to extensive and often challenging medication regimens.

## List of Abbreviations

ACEi	Angiotensin-Converting Enzyme Inhibitor
AF	Atrial Fibrillation
AIC	Akaike Information Criterion
AOR	Adjusted Odds Ratio
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
ASR	Age-Standardized Prevalence Rate
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CVI	Chronic Venous Insufficiency
EF	Ejection Fraction
EMR	Electronic Medical Record
ESC	European Society of Cardiology

HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
IQR	Interquartile Range
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralocorticoid Receptor Antagonist
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
SD	Standard Deviation
SGLT2	Sodium–Glucose Cotransporter 2
T2DM	Type 2 Diabetes Mellitus

## Ethical Clearance

Ethical approval was obtained from the Research Ethics Committee of Gunung Jati General Hospital (No. 060/LAIKETIK/KEPPKRSJG/X/2024). All patient data were anonymized.

## Publication Approval

All authors are consent to the publication of this manuscript.

## Authors Contributions

YPR: conceptualized and designed the study, curated and analyzed the data, interpreted the findings, and drafted the manuscript. WP: contributed to study design, data interpretation, critical review of the manuscript, and refinement of the discussion and conclusions. BBS: provided senior supervision, methodological guidance, and critical revisions for important intellectual content. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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## Conflict of Interest

The authors declare that there are no conflicts of interest.

## Availability of Data and Materials

The analysis data and anonymous data samples are held by the corresponding author and may be accessed with special permission for research purposes.

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## Generative AI and AI-Assisted Technologies in the Writing Process

The author used the DeepL application to assist in writing good English in accordance with scientific language rules. No AI machines were used in writing this manuscript.

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