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Research Article

# Evaluating the Use of Guideline-Recommended Medications and Potentially Inappropriate Medications among Outpatients with Heart Failure

Kittipak Jenghua[1,2*], Sirayut Phatthanasobhon[1,2], Duangkamon Poolpun[3], Panadda Ngamsom[4]

1 Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
2 Pharmacoepidemiology, Social and Administrative Pharmacy (PSAP) Research Unit, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
3 Department of Pharmacy, Buddhachinaraj Hospital, Phitsanulok, Thailand
4 Pharmacy Department, Chiangkham Hospital, Phayao, Thailand.

## ABSTRACT

In heart failure outpatients, it is critical to use guideline-directed medical therapy (GDMT) and avoid potentially inappropriate medications for heart failure (PIMHFs). The study's objective was to investigate GDMT use patterns and rates, as well as PIMHF use prevalence and predictors. Medication prescriptions for HF outpatients between January 1, 2020, and December 31, 2022, were reviewed for GDMT and PIMHF usage. Patterns and rates of GDMT use were determined using current HF recommendations. The prevalence and predictors of PIMHFs, as evaluated by the combined St Vincent, Thai, and Beers criteria, were determined using binary logistic regression analysis and are reported as percentages, adjusted odds ratios (aORs), and 95% confidence intervals (CIs). A total of 541, 242, and 1,110 patients with heart failure and reduced ejection fraction (HFrEF), mildly reduced EF (HFmrEF), and preserved EF (HFpEF), respectively, were included in this study. In HFrEF (31.79%) and HFmrEF (24.38%) patients, triple therapy with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists was most common. However, in HFpEF patients (15.77%), monotherapy with mineralocorticoid receptor antagonists was most common. The overall PIMHF prevalence was 9.03%, with HFpEF (10.72%) having the highest prevalence, followed by HFrEF (7.21%) and HFmrEF (5.37%). The PIMHF predictors were a smaller hospital size (aOR = 1.98, 95% CI = 1.40–2.79), polypharmacy (aOR = 3.15, 95% CI = 1.44–6.90), and hyperpolypharmacy (aOR = 3.80, 95% CI = 2.54–5.68). In clinical practice, HF outpatients may not receive the optimal GDMT pattern. Moreover, PIMHFs are frequently utilized.

**Keywords:**
Heart failure; Appropriate use of medications; Pattern of medication use; Guideline-recommended medications; Potentially inappropriate medications list

## 1. INTRODUCTION

Heart failure (HF) is a chronic condition and global health concern due to its high mortality, hospitalization rate, and medical costs[1]. In Thailand, the annual rate of HF hospitalization was reported to increase from 138 per 100,000 beneficiaries in 2008 to 168 per 100,000 in 2013. Additionally, all-cause rehospitalizations during 2008–2013 remained high and constant, with 1-month and 1-year rehospitalization rates of 34.5% and 73.4%, respectively, in 2013[2].

Medication optimization is an important component of determining efficacy and safety in the care of HF patients, and it is associated with improved health outcomes. To achieve optimum medical therapy, patients with HF must receive medications that reduce mortality risk (guideline-directed medical therapy [GDMT]) while avoiding medications that worsen HF

***Corresponding author**:
* Kittipak Jenghua Email: kittipak.je@up.ac.th

(potentially inappropriate medications for HF [PIMHFs])[3]. To maximize therapeutic impact, multiple GDMT classes—renin-angiotensin system inhibitors (RASIs), which may be angiotensin receptor/neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs), evidence-based beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium glucose cotransporter 2 inhibitors (SGLT2is)—should be taken concurrently, and recommended target doses (TDs) should be achieved[4-6]. Unfortunately, observational studies have shown that the use of GDMT in clinical practice has remained low over time[7-9]. Furthermore, the patients' dosages are still suboptimal[10, 11]. With more clear evidence of GDMT use now available, both current national and international HF guidelines support the use of GDMT in all types of HF, despite differing levels of recommendation[12-16]. In contrast, the use of PIMHFs is likely to be associated with an increased risk of hospitalization in patients with HF. The rates of PIMHF use vary based on the criteria used for PIMHF evaluation, ranging from 14.6% to 54%[17-19].

In clinical practice, HF outpatients are typically managed by general practitioners rather than cardiologists because they frequently have various comorbidities that necessitate numerous medical specializations. Furthermore, not all HF patients' medication use is thoroughly evaluated, increasing the possibility of an improper prescription of GDMT as well as PIMHFs. Currently, no data exist on the use of GDMT based on the most recent HF guidelines or PIMHFs in patients with each type of HF. The purpose of this study was to evaluate GDMT use patterns and rates based on current HF recommendations, as well as PIMHF prevalence and predictors, among outpatients with all forms of HF

## 2. MATERIALS AND METHODS

### 2.1 Study design and setting

A cross-sectional descriptive study was conducted at two public hospitals in northern Thailand: a secondary-care hospital (231 beds) in Phayao Province and a tertiary-care hospital (1,063 beds) in Phitsanulok Province. The two study hospitals are academic and referral institutions, and they provide a comprehensive electronic medical record (EMR) database with information on patient characteristics, diagnoses, laboratory results and both outpatient and inpatient prescriptions. The secondary-care hospital had one cardiologist at the time of the study, whereas the tertiary-care hospital had six. Although the HF clinic operated in both hospitals, it only served HF patients who met specific criteria. These criteria included individuals with an LVEF of ≤40%, frequent hospitalizations, multiple medications, and poor adherence. As a result, most HF outpatients in both hospitals did not attend the HF clinic and received care from general practitioners rather than cardiologists.

The present study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[20].

### 2.2 Participants

All patients with an HF diagnosis who visited the outpatient department (OPD) between January 1, 2020, and December 31, 2022, were included in this study. HF was identified using the following International Classification of Diseases, 10th revision (ICD-10) codes: I11.0, I13.0, I13.2, I50, I50.0, I50.1 and I50.9[2]. Patients without a report of left ventricular ejection fraction (LVEF), those under the age of 18 and those without information on medication prescriptions were excluded from this study.

### 2.3 Data source and collection

Data from 2020–2022 were gathered from EMR databases and classified according to demographic information, clinical results, laboratory findings and prescription features. To evaluate each patient's recent GDMT regimens based on their HF type, we used the most recent LVEF (which may be prior to 2020) to determine their HF type. There were three main types of HF: HF with reduced ejection fraction (HFrEF, LVEF ≤40%), HF with mildly reduced EF (HFmrEF, LVEF = 41%–49%), and HF with preserved EF (HFpEF, LVEF ≥50%)[13]. The patients in the HFmrEF group might be those with HF and improved EF (HFimpEF). These patients have a history of HFrEF, but their EF has increased by 10% or more, resulting in an LVEF greater than 40%. Chronic comorbidities were identified using the acknowledged ICD-10 coding algorithm[21], and the comorbidity score for each participant was calculated using the Charlson Comorbidity Index (CCI)[22, 23]. The three-year study period (2020-2022) was chosen so that each participant would have many prescriptions to be examined for both GDMT and PIMHF use. To ensure that the medications being evaluated were PIMHFs, each participant was assigned an index date, which was defined as the date when an HF diagnosis was first recorded on the database in 2020–2022, and medications prescribed from the index date until the end of 2022 were evaluated for PIMHF use. We reviewed all OPD prescriptions for each patient to assess their use of GDMT and PIMHFs. To identify recent GDMT regimens, we considered only the most recent prescription for each GDMT drug

**Table 1** Characteristics of the study patients according to their HF type

| Characteristics | Total (n = 1,893) | HFrEF (n = 541) | HFmrEF (n = 242) | HFpEF (n = 1,110) | P-value |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 898 (47.44) | 342 (63.22) | 129 (53.31) | 427 (38.47) | < 0.001 |
| Female | 995 (52.56) | 199 (36.78) | 113 (46.69) | 683 (61.53) | |
| Age (year) | 67.38 ± 14.50 | 63.44 ± 14.93 | 66.45 ± 15.26 | 69.51 ± 13.68 | < 0.001 |
| <60 | 530 (28.00) | 212 (39.19) | 73 (30.17) | 245 (22.07) | < 0.001 |
| ≥60 | 1,363 (72.00) | 329 (60.81) | 169 (69.83) | 865 (77.93) | |
| Health insurance | | | | | |
| UCS | 1,433 (75.70) | 415 (76.71) | 187 (77.27) | 831 (74.86) | < 0.001 |
| CSMBS | 351 (18.54) | 77 (14.23) | 40 (16.53) | 234 (21.08) | |
| SSS | 84 (4.44) | 37 (6.84) | 14 (5.79) | 33 (2.97) | |
| Self-payment | 25 (1.32) | 12 (2.22) | 1 (0.41) | 12 (1.08) | |
| Number of chronic comorbidities | 2 (1-3) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 0.01 |
| 1 | 690 (36.45) | 199 (36.78) | 81 (33.47) | 410 (36.94) | < 0.001 |
| 2 | 465 (24.56) | 148 (27.36) | 65 (26.86) | 252 (22.70) | |
| ≥3 | 619 (32.70) | 181 (33.46) | 87 (35.95) | 351 (31.52) | |
| Types of chronic comorbidities | | | | | |
| Hypertension | 673 (35.55) | 167 (30.87) | 81 (33.47) | 425 (38.29) | 0.01 |
| Atrial fibrillation | 333 (17.59) | 84 (15.53) | 53 (21.90) | 196 (17.66) | 0.096 |
| Chronic kidney disease, mild to moderate | 326 (17.22) | 92 (17.01) | 30 (12.40) | 204 (18.38) | 0.082 |
| Diabetes without complications | 320 (16.90) | 96 (17.74) | 40 (16.53) | 184 (16.58) | 0.826 |
| Myocardial infarction | 127 (6.71) | 50 (9.24) | 24 (9.92) | 53 (4.77) | < 0.001 |
| Chronic pulmonary disease | 72 (3.80) | 20 (3.70) | 6 (2.48) | 46 (4.14) | 0.466 |
| Alcohol misuse | 63 (3.33) | 21 (3.88) | 11 (4.55) | 31 (2.79) | 0.27 |
| Chronic kidney disease, severe | 60 (3.17) | 13 (2.40) | 10 (4.13) | 37 (3.33) | 0.394 |
| Diabetes with complications | 59 (16.90) | 12 (2.22) | 8 (3.31) | 39 (3.51) | 0.358 |
| Liver disease, mild | 55 (2.91) | 13 (2.40) | 11 (4.55) | 31 (2.79) | 0.242 |
| Stroke or transient ischaemic attack | 54 (2.85) | 14 (2.59) | 10 (4.13) | 30 (2.70) | 0.437 |
| Chronic pain | 48 ((2.54) | 5 (0.92) | 6 (2.48) | 37 (3.33) | 0.014 |
| Hypothyroidism | 45 (2.38) | 7 (1.29) | 6 (2.48) | 32 (2.88) | 0.137 |
| Cirrhosis | 42 (2.22) | 11 (2.03) | 5 (2.07) | 26 (2.34) | 0.909 |
| Cancer, non-metastatic | 30 (1.58) | 10 (1.85) | 2 (0.83) | 18 (1.62) | 0.565 |
| Comorbidity score | 1 (1-2) | 1 (1-2) | 1 (1-2) | 1 (1-2) | 0.615 |
| 1 | 1,097 (57.95) | 299 (55.27) | 140 (57.85) | 658 (59.28) | 0.301 |
| ≥2 | 796 (42.05) | 242 (44.73) | 102 (42.15) | 452 (40.72) | |
| Patient prescriptions | | | | | |
| Number of prescriptions/patients | 2 (1-9) | 2 (1-7) | 3 (1-9) | 2 (1-11) | 0.578 |
| Polypharmacy | 1,345 (71.05) | 419 (77.45) | 166 (68.60) | 760 (68.47) | 0.001 |
| Hyperpolypharmacy | 674 (35.60) | 188 (34.75) | 91 (37.60) | 395 (35.59) | 0.743 |
| Laboratory results | | | | | |
| SBP (mmHg) | 130.66 ± 26.64 | 126.64 ± 24.26 | 132.80 ± 27.45 | 132.18 ± 27.38 | < 0.001 |
| DBP (mmHg) | 73.51 ± 17.21 | 76.54 ± 17.14 | 75.54 ± 17.96 | 71.58 ± 16.83 | < 0.001 |
| HR (bpm) | 84.31 ± 18.86 | 86.13 ± 19.37 | 85.83 ± 19.01 | 83.10 ± 18.49 | 0.004 |
| FBS (mg/dL) | 127.39 ± 72.56 | 131.10 ± 70.92 | 123.06 ± 58.11 | 126.47 ± 75.85 | < 0.001 |
| HbA1C (mg%) | 7.19 ± 1.97 | 7.12 ± 1.90 | 6.86 ± 1.36 | 7.33 ± 2.15 | < 0.001 |
| eGFR (mL/minute/1.73 $m^2$) | 59.48 ± 29.03 | 62.17 ± 28.85 | 57.87 ± 30.10 | 58.41 ± 28.85 | 0.057 |
| Serum potassium (mg/dL) | 4.14 ± 0.63 | 4.11 ± 0.57 | 4.11 ± 0.61 | 4.16 ± 0.66 | < 0.001 |
| HF medications | | | | | |
| Diuretics | 1,095 (57.84) | 366 (67.65) | 137 (56.61) | 592 (53.33) | < 0.001 |
| BBs | 888 (46.91) | 360 (66.54) | 134 (55.37) | 394 (35.50) | < 0.001 |
| MRAs | 569 (30.06) | 246 (45.47) | 83 (34.30) | 240 (21.62) | < 0.001 |
| ACEIs | 568 (30.01) | 230 (42.51) | 93 (38.43) | 245 (22.07) | < 0.001 |
| ARBs | 380 (20.07) | 112 (20.70) | 45 (18.60) | 223 (20.09) | 0.793 |
| Digoxin | 133 (7.03) | 57 (10.54) | 18 (7.44) | 58 (5.23) | < 0.001 |
| Isosorbide dinitrate + hydralazine | 52 (2.75) | 22 (4.07) | 6 (2.48) | 24 (2.16) | 0.088 |
| SGLT2is | 21 (1.11) | 6 (1.11) | 3 (1.24) | 12 (1.08) | 0.95 |
| ARNIs | 10 (0.53) | 7 (1.29) | 0 (0.00) | 3 (0.27) | 0.013 |
| Ivabradine | 3 (0.16) | 3 (0.55) | 0 0 (0.00) | 0 (0.00) | 0.039 |
| GDMT allergy or intolerance | 27 (1.43) | 7 (1.29) | 6 (2.48) | 14 (1.26) | 0.334 |
| Enalapril | 22 (1.16) | 7 (1.29) | 5 (2.07) | 10 (0.90) | 0.292 |
| Losartan | 3 (0.16) | 0 (0.00) | 1 (0.41) | 2 (0.18) | 0.360 |
| Bisoprolol or carvedilol | 2 (0.11) | 0 (0.00) | 1 (0.41) | 1 (0.09) | 0.321 |
| Spironolactone | 1 (0.05) | 0 (0.00) | 0 (0.00) | 1 (0.09) | 1.000 |

All laboratory values and ages are presented as the means ± standard deviations (SDs). The number of prescriptions per patient, chronic comorbidities and comorbidity score are presented as the medians and interquartile ranges ($Q_1$-$Q_3$). Categorical variables are presented as frequencies with percentages. The P value indicates the comparison of the three HF types.

Patients with at least one such prescription were assigned to the polypharmacy (≥five medications/prescription) or hyperpolypharmacy (≥ten medications/prescription) group.

The most recently recorded SBP, DBP, HR, FBS, HbA1c, eGFR, and serum potassium values were available for 1,869, 1,881, 878, 357, 1,532 and 1,515 patients, respectively.

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor/neprilysin inhibitors; BBs, beta-blockers; CSMBS, Civil Servant Medical Benefit Scheme; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1C, haemoglobin A1C; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MRAs, mineralocorticoid receptor antagonists; SBP, systolic blood pressure; SGLT2is, sodium glucose cotransporter 2 inhibitors; SSS, Social Security Scheme; UCS, Universal Health Coverage Scheme.

ARNI includes sacubitril/valsartan. ACEIs include enalapril, captopril, ramipril, and perindopril. ARBs include losartan, valsartan, azilsartan, and telmisartan. BBs include carvedilol and bisoprolol. MRAs include spironolactone. SGLT2is include dapagliflozin and empagliflozin.

in terms of receipt and dosage optimization. GDMT- and PIMHF-related drugs were identified using the hospitals' drug codes. Specialists at the hospitals' data centres retrieved the data from the database.

The use of GDMT was evaluated using current HF recommendations derived from current guidelines and updates, including the Heart Failure Council of Thailand (HFCT) guidelines[13, 15, 24, 25], the European Society of Cardiology (ESC) guidelines[12, 16] and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines[14]. Supplemental Table 1 provides a summary of GDMT use recommendations according to each guideline. Only evidence-based BBs, such as carvedilol, bisoprolol, metoprolol succinate, and nebivolol, were evaluated for this study. The dosages of GDMT drugs were examined for dose optimization based on the national HF guidelines[24, 25]. GDMT drugs were discovered to be available for use in each of the study hospitals during the study period, despite the fact that both ARNIs and SGLT2is are not included in the national list of essential medicines (NLEM).

Three sets of HF-related PIM criteria were utilized to identify PIMHFs: the 2014 St Vincent criteria[17], the 2021 Thai criteria[26] and the 2023 Beers criteria (the drug-HF interaction category)[27]. All the criteria are explicit and include a list of drugs that may exacerbate HF. Except for non-dihydropyridine calcium channel blockers (non-DHP CCBs), which are only for HFrEF, all other PIMHFs are for all HF types. The St Vincent criteria include 11 medications or medication classes, the Beer criteria include 6 medications or medication classes, and the Thai criteria include 47 medications. The combination of the three criteria resulted in 73 PIMHFs (42, 47, and 19 PIMHFs were extracted from the St Vincent, Thai, and Beers criteria, respectively). Of the extracted PIMHFs, 57 could be assessed, yielding 78.08% coverage.

### 2.4 Statistical analysis

Normally distributed continuous variables are reported as the means ± standard deviations (SDs), and analysis of variance (ANOVA) was performed to compare the three HF types. Nonnormally distributed continuous variables are reported as medians and interquartile ranges (IQRs), and the Kruskal–Wallis test (K-W test) was used to compare the three HF types. Categorical variables are reported as frequencies and percentages, and the chi-square test or Fisher's exact test was used to compare the three HF types, as appropriate.

Each HF type was analysed separately. The GDMT use patterns were classified as no, mono, dual, triple, or quadruple therapy, with the rate of each subpattern determined. Only HFrEF patients had a GDMT drug dose (SGLT2i up-titration not required) classified as less than 50%, 50–99% or 100%. The rate of PIMHF usage was calculated for the three combined criteria as well as for each set of criteria individually. Individual PIMHF distributions are also reported.

A binary logistic regression analysis was used to calculate crude odds ratios (crude ORs), adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the PIMHF predictors. In the univariate analysis, variables with P values less than 0.2 were included in the adjusted analysis. The variance inflation factors (VIFs) were calculated for each factor to detect multicollinearity (two independent variables that are highly linked). Factors with a VIF ≥5 were excluded from the model[28]. The independent predictors were selected using a backward elimination strategy (the item with the least significance was removed at each stage until all remaining factors in the model had a P value less than 0.05). STATA 18.0 (StataCorp LLC, College Station, TX, USA) was used to perform all the statistical analyses. All hypothesis tests were two-tailed. P values less than 0.05 were regarded as statistically significant.

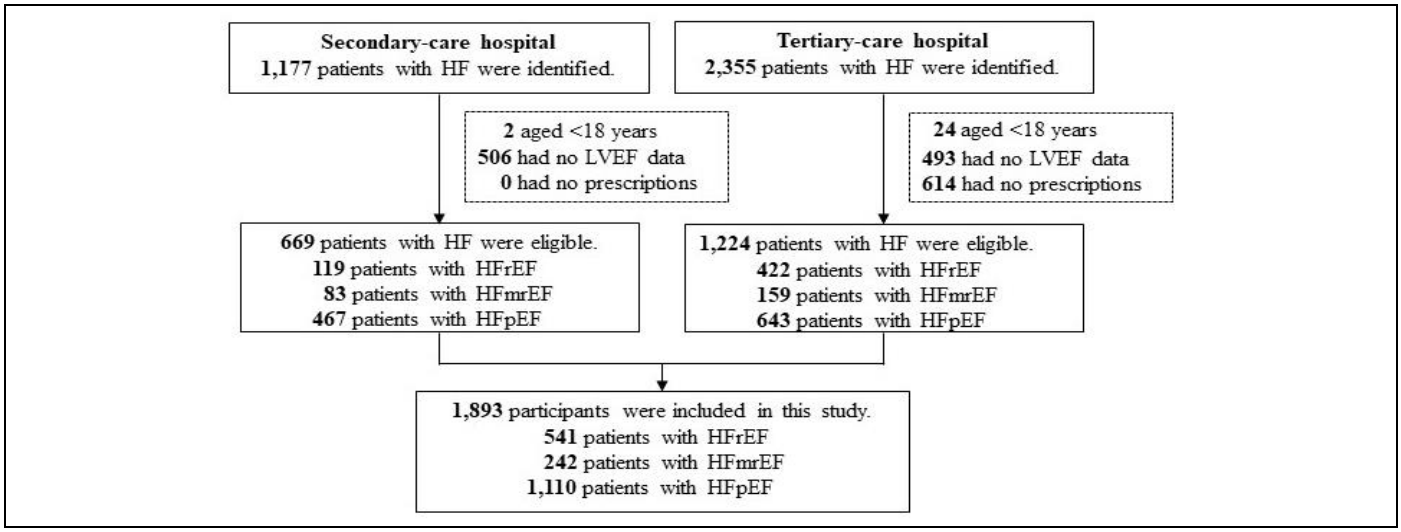



**Figure 1.** Patient recruitment process

**Table 2** PIMHF distribution from three sets of HF-related criteria

| PIMHF | St Vincent criteria | Thai criteria | Beers criteria | Total* (n = 1,893) | HFrEF (n = 541) | HFmrEF (n = 242) | HFpEF (n = 1,110) |
|---|---|---|---|---|---|---|---|
| **Prescribed any PIMHF** | | | | | | | |
| Combined criteria | | | | 171 (9.03) | 39 (7.21) | 13 (5.37) | 119 (10.72) |
| St Vincent criteria | | | | 160 (8.45) | 38 (7.02) | 11 (4.55) | 111 (10.00) |
| Thai criteria | | | | 153 (8.08) | 37 (6.84) | 11 (4.55) | 105 (9.46) |
| Beers criteria | | | | 54 (2.85) | 14 (2.59) | 1 (0.41) | 39 (3.51) |
| **25 prescribed PIMHFs** | | | | | | | |
| Prednisolone, oral | ● | ● | | 91 (4.81) | 22 (4.07) | 7 (2.89) | 62 (5.59) |
| Naproxen | ● | ● | ● | 20 (1.06) | 4 (0.74) | 1 (0.41) | 15 (1.35) |
| Pioglitazone | ● | ● | ● | 18 (0.95) | 8 (1.48) | 0 (0.00) | 10 (0.90) |
| Methotrexate | | ● | | 13 (0.69) | 3 (0.55) | 2 (0.83) | 8 (0.72) |
| Ibuprofen | ● | ● | ● | 9 (0.48) | 1 (0.18) | 0 (0.00) | 8 (0.72) |
| Piperacillin sodium + Tazobactam sodium, injection | ● | | | 9 (0.48) | 1 (0.18) | 0 (0.00) | 8 (0.72) |
| Sodium phosphates solution | ● | | | 5 (0.26) | 0 (0.00) | 1 (0.41) | 4 (0.36) |
| Meloxicam | ● | | ● | 3 (0.16) | 0 (0.00) | 0 (0.00) | 3 (0.27) |
| Dexamethasone, oral | ● | ● | | 3 (0.16) | 0 (0.00) | 1 (0.41) | 2 (0.18) |
| Clozapine | | ● | | 3 (0.16) | 0 (0.00) | 0 (0.00) | 3 (0.27) |
| Diclofenac | ● | ● | ● | 2 (0.11) | 1 (0.18) | 0 (0.00) | 1 (0.09) |
| Celecoxib | ● | ● | ● | 2 (0.11) | 0 (0.00) | 0 (0.00) | 2 (0.18) |
| Metformin (for poor renal function) | ● | | | 2 (0.11) | 0 (0.00) | 0 (0.00) | 2 (0.18) |
| Prazosin | | ● | | 2 (0.11) | 0 (0.00) | 0 (0.00) | 2 (0.18) |
| Diltiazem immediate release (for HFrEF) | ● | ● | ● | 1 (0.05) | 1 (0.18) | - | - |
| Verapamil (for HFrEF) | ● | ● | ● | 1 (0.05) | 1 (0.18) | - | - |
| Salbutamol, oral | ● | ● | | 1 (0.05) | 0 (0.00) | 0 (0.00) | 1 (0.09) |
| Cyclophosphamide | | ● | | 1 (0.05) | 1 (0.18) | 0 (0.00) | 0 (0.00) |
| Paclitaxel | | ● | | 1 (0.05) | 0 (0.00) | 1 (0.41) | 0 (0.00) |
| Itraconazole | ● | | | 1 (0.05) | 1 (0.18) | 0 (0.00) | 0 (0.00) |
| Azithromycin, injection | ● | | | 1 (0.05) | 1 (0.18) | 0 (0.00) | 0 (0.00) |
| Metronidazole, injection | ● | | | 1 (0.05) | 0 (0.00) | 1 (0.41) | 0 (0.00) |
| Polyethylene glycol powder for solution | ● | | | 1 (0.05) | 0 (0.00) | 0 (0.00) | 1 (0.09) |
| Pseudoephedrine | ● | ● | | 1 (0.05) | 0 (0.00) | 0 (0.00) | 1 (0.09) |
| Ergotamine + caffeine | | ● | | 1 (0.05) | 0 (0.00) | 0 (0.00) | 1 (0.09) |
| **Total** | **19** | **17** | **8** | **25** | **12** | **7** | **18** |

*Listed by frequency in descending order.

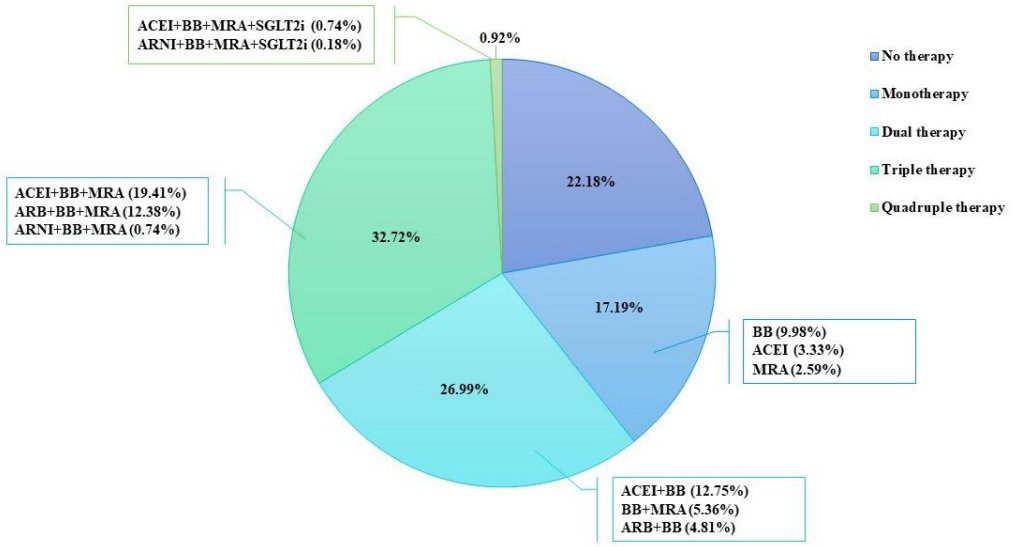
## 3. RESULTS

### 3.1 Patient characteristics

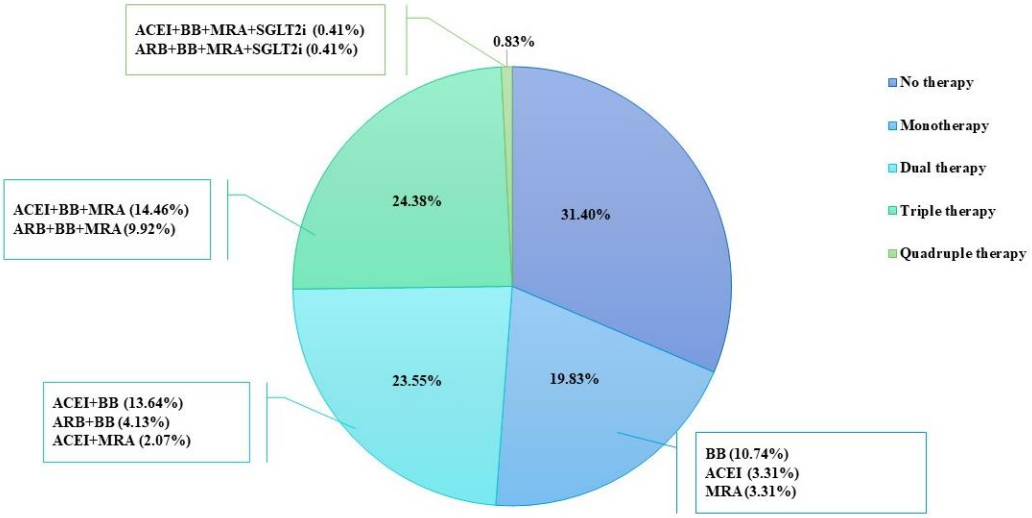
Figure 1 shows the patient recruitment process. This study included 1,893 eligible patients: 541, 242 and 1,110 patients with HFrEF, HFmrEF and HFpEF, respectively. Table 1 shows the characteristics of the participants according to their HF type. The patients were primarily female (52.56%), with an average age of 67.38 ± 14.50 years. Most patients (93.71%) had at least one chronic comorbidity, with hypertension (35.55%) being the most prevalent, followed by atrial fibrillation (17.59%) and mild to moderate chronic kidney disease (CKD) (17.22%). Based on the laboratory results, the patients exhibited clinical stability, with a mean systolic and diastolic blood pressure and heart rate of 130.66 ± 26.64 mmHg, 73.51 ± 17.21 mmHg, and 84.31 ± 18.86 bpm, respectively. Additionally, they were not contraindicated for GDMT, as indicated by an estimated glomerular filtration rate and serum potassium of 59.48 ± 29.03 mL/min/1.73 $m^2$ and 4.14 ± 0.63 mg/dL, respectively. All the HF medication groups were prescribed, with diuretics (57.8%) being the most common, followed by BBs (46.9%) and MRAs (30.1%). SGLT2is (1.11%) and ARNIs (0.53%) were slightly prescribed. A minor percentage of patients (1.43%) had a history of GDMT allergy or intolerance, with enalapril (1.16%) being the most reported.

A comparison of HF types revealed statistically significant differences in some attributes. Patients with HFpEF were predominantly female and older than those with other types of HF. Despite no statistically significant difference in a variety of chronic comorbidities, HFrEF and HFmrEF patients were more likely to have myocardial infarction, whereas HFpEF patients were more likely to have mild to moderate CKD, chronic pain, chronic lung illness, cirrhosis, and hypertension.

(A) Patients with HFrEF (n = 541)




(B) Patients with HFmrEF (n = 242)




(C) Patients with HFpEF (n = 1,110)

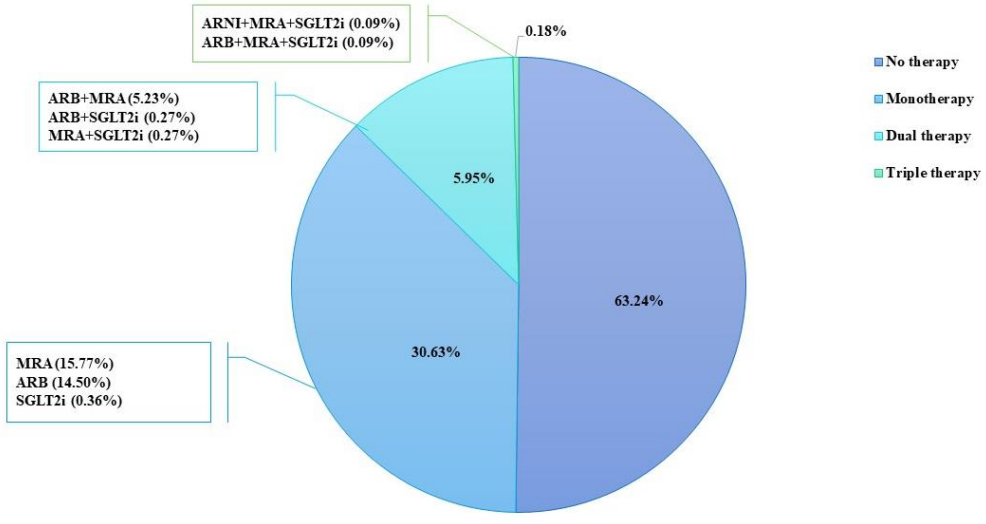



**Figure 2**. GDMT use pattern and rate by HF type

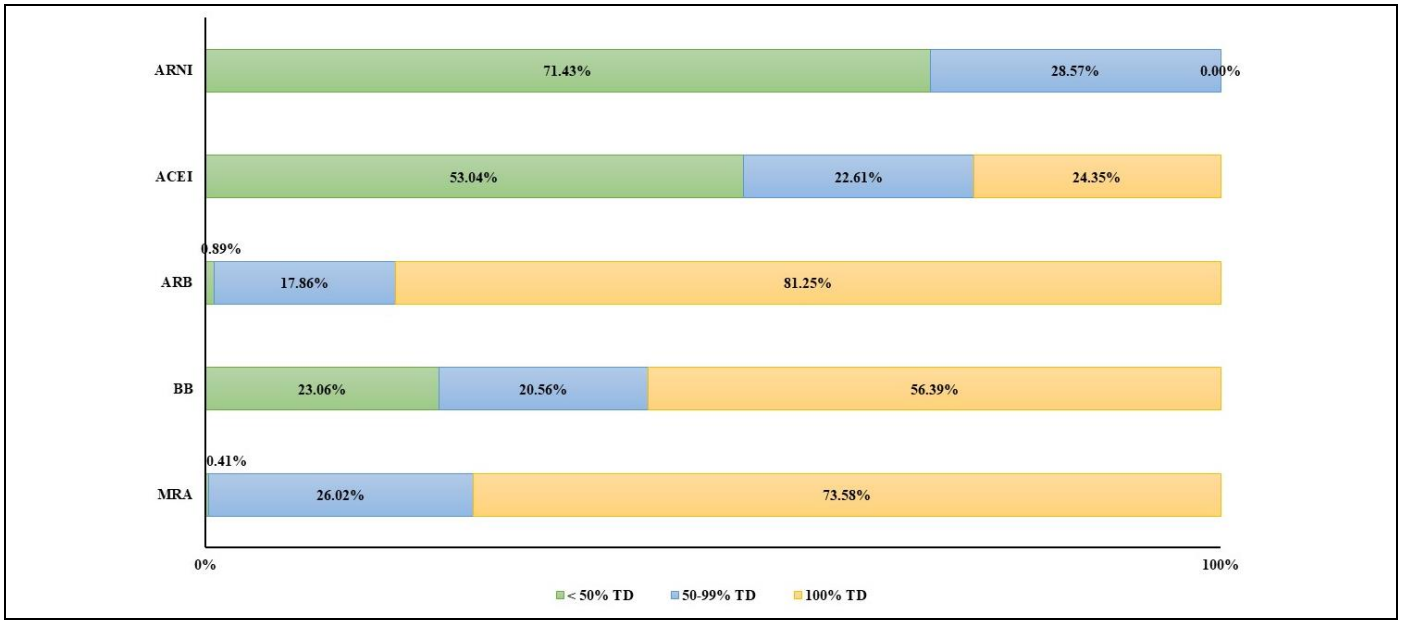



**Figure 3**. Percentages of HFrEF patients who received the recommended target doses within each GDMT class

### 3.2 Patterns and rates of guideline-directed medical therapy

Figure 2 depicts the typical patterns and rates of GDMT usage by HF type. Supplemental Table 2 lists every GDMT pattern utilized by HF type. In all, 47.44% of patients (22.18% for HFrEF, 31.40% for HFmrEF and 63.24% for HFpEF) were not on any GDMT drugs.

Figure 2(A) shows that, of the HFrEF patients, 0.92% received quadruple therapy, whereas 32.72%, 26.99% and 17.19% received triple, dual, and monotherapy, respectively. The most common treatment pattern was triple therapy with ACEIs/ARBs, BBs and MRAs (31.79%). Only a small proportion of patients received ARNI (1.29%) or SGLT2i (1.11%) regimens. According to Figure 2(B), only 0.83% of the HFmrEF patients received quadruple therapy, whereas 24.38%, 23.55% and 19.83% received triple, dual, and monotherapy, respectively, with triple therapy with ACEIs/ARBs, BBs and MRAs being the most common (24.38%). Figure 2(C) demonstrates that only 0.18% of the HFpEF patients received triple therapy, while 5.95% and 30.63% received dual therapy and monotherapy, respectively. Monotherapy with MRAs was the most common pattern (15.77%).

Figure 3 displays the percentage of HFrEF patients who received less than 50%, 50–99% or 100% the TD for each GDMT class. The percentage of patients who received 100% the TD was highest in the ARB group (81.25%) and lowest in the ARNI group (0.00%). The proportion of patients with less than 50% the TD was the highest in the ARNI group (71.43%), followed by the ACEI group (53.04%).

### 3.3 Prevalence and predictors of potentially inappropriate medications for heart failure

Table 2 displays the prevalence of PIMHF use as well as the individual PIMHFs for each HF type. Patients were prescribed 25 of the 57 PIMHFs evaluated (Supplemental Table 3). According to the combined criteria, any PIMHF was administered to 171 (9.03%) patients, with the highest prevalence found among HFpEF patients (10.72%), followed by HFrEF (7.21%) and HFmrEF (5.37%) patients. When each set of criteria was applied, the St Vincent, Thai, and Beers criteria yielded patient percentages of 8.45%, 8.08% and 2.85%, respectively. The PIMHF prevalence was greater in the secondary-care hospital than in the tertiary-care hospital (15.99% vs. 5.23%, P value < 0.001). The most often administered PIMHF was prednisolone (4.81%), followed by naproxen (1.06%), pioglitazone (0.95%), methotrexate (0.69%), and ibuprofen (0.48%). HFpEF patients used more PIMHFs (18 items) than HFrEF (12 items) or HFmrEF (7 items) patients. However, the most administered PIMHFs appeared to be similar in all three types of HF.

Table 3 shows the results of univariate and multivariate analyses of the PIMHF predictors. According to the univariate analysis, multiple characteristics predicted PIMHF use, but only hospital type, polypharmacy, and hyperpolypharmacy were found to be independent predictors. Compared with the tertiary-care hospital, the secondary-care hospital had an odds ratio of 1.98 (95% CI: 1.40−2.79). Polypharmacy had an odds ratio of 3.15 (95% CI: 1.44–6.90) compared to nonpolypharmacy. Compared with nonhyper-polypharmacy, hyperpolypharmacy had an odds ratio of 3.80 (95% CI: 2.54–5.68).

**Table 3** Factors associated with PIMHF use (n = 1,893)

| Factors | Crude OR (95% CI), P-value* | Adjusted OR (95% CI), P-value |
|---|---|---|
| Secondary-care hospital | 3.45 (2.49 – 4.78), < 0.001 | 1.98 (1.40 – 2.79), < 0.001 |
| Female | 1.14 (0.83 – 1.57), 0.411 | - |
| Older patients (age ≥ 60 years) | 0.80 (0.57 – 1.13), 0.204 | - |
| HFmrEF | 0.73 (0.38 – 1.40), 0.342 | - |
| HFpEF | 1.55 (1.06 – 2.25), 0.024 | - |
| UCS | 0.98 (0.68 – 1.42), 0.933 | - |
| Polypharmacy | 9.31 (4.54 – 19.07), < 0.001 | 3.15 (1.44 – 6.90), 0.004 |
| Hyperpolypharmacy | 6.63 (4.62 – 9.53), < 0.001 | 3.80 (2.54 – 5.68), < 0.001 |
| Number of comorbidities | 1.38 (1.24 – 1.52), < 0.001 | - |
| Comorbidity score ≥2 | 3.14 (2.25 – 4.38), < 0.001 | - |

*Factors with a P value less than 0.2 were included in the multivariate analysis.

## 4. DISCUSSION

This study assessed GDMT and PIMHF use in individuals with each HF type. HFrEF and HFmrEF patients often received triple therapy comprising ACEIs/ARBs, BBs, and MRAs, but HFpEF patients usually received monotherapy with MRAs. PIMHFs were mostly given to HFpEF patients; however, all three types of patients received PIMHFs. This study indicated that the use of GDMT and PIMHFs in clinical practice has potential for improvement.

### 4.1 Patterns and rates of guideline-directed medical therapy

The renin-angiotensin-aldosterone system and sympathetic nervous system are activated less with increasing LVEF, with a 50% mortality benefit cut-off; hence, HFmrEF patients respond better to neurohormonal therapy than HFpEF patients[29, 30]. Current HF guidelines recommend all GDMT classes in HFrEF and HFmrEF patients, despite differing levels of recommendation, but BBs and ACEIs are not currently recommended as GDMTs for HFpEF patients.

The four GDMT classes work synergistically in HFrEF treatment; consequently, the more GDMT classes are used concurrently, the greater the therapeutic benefits. According to a network meta-analysis by Tromp et al.[6], the reduction in all-cause mortality varies based on the pharmacological treatment combinations, with quadruple therapy comprising ARNIs, BBs, MRAs, and SGLT2is being the most beneficial. Our data followed a trend similar to that of Wirtz et al.[7], who reported that 23%, 22%, 41%, and 13% of patients received no, mono, dual, and triple therapy, respectively. However, that study indicated dual therapy as a prevalent trend, whereas our analysis found triple therapy to be a common pattern. Our findings were comparable to those of a previous global survey[9], which revealed that 37% of discharged patients and 34% of survivors received triple therapy with RASIs, BBs, and MRAs at 6 months. However, our sample showed minimal use of ARNIs and SGLT2is, both of which are considered class I drugs. Sacubitril/valsartan (ARNI) is recommended for treating HFrEF as a substitute for an ACEI or ARB, as well as in patients who are ACEI or ARB naïve[13]. Recent real-world investigations revealed a somewhat higher rate of ARNI use among patients with HFrEF, ranging from 8% to 12.6%[31, 32]. Despite various possible hurdles to ARNI use[32, 33], the cost and accessibility of ARNIs and SGLT2is appear to be the most important reasons leading to Thailand's low utilization rate. GDMT prices vary widely between countries with different income levels, with ARNIs being the most expensive. Many low- and middle-income countries do not offer ARNIs or SGLT2is through publicly funded pharmaceutical programs that reduce prices for qualified patients[34]. Our patients with primary UCS rarely use ARNIs or SGLT2is because they are not on the NLEM. Nonetheless, given these limitations, the best potential GDMT pattern for patients is ACEIs/ARBs, BBs, and MRAs. Our findings were comparable with those of Hadidi et al.[11], who reported suboptimal dosages of drugs in the GDMT class, particularly ARNIs and ACEIs. Importantly, obtaining the suggested target dose is critical for treating HFrEF since this dose is likely to result in additional therapeutic benefits. Therefore, it is crucial to meet the target dose, even if symptoms improve at lower dosages[5, 35].

With increasing amounts of data on the use of GDMT in patients with HFmrEF, the current guidelines recommend the same approach as that used for patients with HFrEF. Stolfo et al.[36] corroborated the outcome of minimum therapy with ACEIs or ARBs combined with BBs in patients with HFmrEF and reported that RASIs or ARNIs combined with BBs were independently related to a decreased risk of cardiovascular mortality, hospitalization for HF, and all-cause mortality. Our HFmrEF patients typically exhibited this trend, which is consistent with the findings of the abovementioned studies.

In contrast to those for HFrEF and HFmrEF, there is no clear evidence for specific disease-modifying therapy for patients with HFpEF. Except for SGLT2is, GDMT classes are considered poor recommendations, with BBs and ACEIs not recommended for patients with

HFpEF according to the current guidelines. Because of the risk of symptomatic bradycardia, BBs should be administered with caution in patients with HFpEF. Arnold et al.[37] reported that BB use increased the probability of hospitalization for HF or mortality, particularly when the LVEF increased.

In outpatients with recent hospitalizations due to HF and those with de novo HF, GDMT can be started at a low dose and rapidly titrated every 1 to 2 weeks, with the goal of administering all four primary classes of therapy at the target dose[4, 38]. Even though the simultaneous start of all four GDMT drug classes is presented as a novel approach, sequential initiation appears to be the preferred method among practitioners, beginning with ACEIs or ARBs, followed by BBs, MRAs and SGLT2is[39]. There is no unique hierarchical sequencing strategy in current clinical practice. Several factors must be considered when starting GDMT. ACEIs, ARBs, and SGLT2is, for example, should be started in HF patients with chronic kidney disease with or without type 2 diabetes mellitus to reduce progressive renal dysfunction and cardiovascular morbidity and mortality, whereas BBs should be started in HF patients with AF[4].

### 4.2 Prevalence and predictors of potentially inappropriate medications for heart failure

Previous studies on PIMHF use have differed because of differences in patient characteristics and the criteria used. Our outpatients had a lower rate of PIMHF use than did both inpatients and outpatients in the study by Jenghua et al.[18] (8.08% vs. 33.03%, respectively, based on the Thai criteria alone). This could be because some PIMHFs, including anticancer agents, oral corticosteroids, and pharmaceutical formulations with a high salt content, are less frequently administered to outpatients. Even though the St Vincent criteria include fewer PIMHFs than do the Thai criteria, some common PIMHF groups are missing from the other criteria, such as medicinal preparations with high sodium contents, oral beta2-agonists, and antifungals. Oral corticosteroids, NSAIDs, COX-2 inhibitors, pioglitazone, and methotrexate were the most prevalent PIMHFs discovered in our analysis, consistent with earlier data[11, 17, 18, 40]. It is recommended that a combination of HF-related PIM criteria or instruments be used in drug use reviews, as each suggests distinct PIMHFs.

### 4.3 Advantages

In this study, we reported on both GDMT and PIMHFs for each of the three HF types. We analysed GDMT usage using the most recent recommendations from the current HF guidelines. Furthermore, we reported the prevalence of PIMHF use as determined by the three combined HF-related PIM criteria, which included up to 73 PIMHFs.

### 4.4 Limitations

This study has several limitations. First, due to the data constraints inherent in retrospective research, this study did not assess the eligibility of individual patients for GDMT use, considering various factors such as drug allergies, intolerances, contraindications, and clinical instability, nor did it consider whether the patients received GDMT from other sources. Therefore, considering these factors could have led to higher utilization rates of GDMT than those reported in this study. Second, because only recently prescribed GDMT was reviewed, changes in drug choices and doses could not be evaluated; for example, patients may have experienced intolerability of an ACEI and were subsequently given an ARB instead. Third, several PIMHFs were not available at the two study hospitals; therefore, this study was unable to investigate them. Finally, PIMHF usage was investigated only in HF patients with confirmed LVEF. PIMHFs may be administered to HF patients with an unknown LVEF. As a result, PIMHF use may be more prevalent in individuals with HF than indicated in our study. Further research should focus on a prospective evaluation of GDMT and PIMHF use, considering the specific reasons for not prescribing GDMT as well as the prescription of PIMHFs.

## 5. CONCLUSIONS

Outpatients with each HF type underutilized optimal GDMT therapy while frequently receiving PIMHFs. A drug use review should be performed periodically in HF patients to verify that the patients receive optimum GDMT and are not prescribed PIMHFs. To promote the prescription of optimal GDMT patterns and the discontinuation of PIMHFs, clinical pharmacists should verify information on allergies, intolerances, contraindications, and recommended dosages for GDMT. Additionally, they should suggest alternative treatments for HF outpatients instead of PIMHFs.

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**Conflict of interest**

The authors declared that they have no competing interests.

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**Ethics approval**
Prior to data collection, the study protocol was reviewed and certified by the Human Ethics Committee of the University of Phayao (study code: UP-HEC 1.1/001/66, approval date: October 31, 2022) and the institutional review boards of the study hospitals (study code: 0015/2565, approval date: December 8, 2022 for the secondary-care hospital and study code: HREC No. 032/2566, approval date: February 27, 2023 for the tertiary-care hospital).

**Author contribution**
Conceptualization, K.J.; Data collection, K.J., S.P., D.P. and P.N.; Formal analysis, K.J. and S.P.; Interpretation, K.J. and S.P.; Writing–original draft, K.J.; Writing–review & editing K.J. All authors approved the final manuscript.

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