

Use of potentially inappropriate medications for heart failure according to the three sets of heart failure-specific criteria in Thai older patients with heart failure

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ABSTRACT

OBJECTIVE To study the prevalence of potentially inappropriate medications for patients with heart failure (PIMHF) use and to identify factors associated with PIMHF use in Thai older HF patients.

METHODS This cross-sectional analytical survey included data on older (≥ 60 years) HF patients obtained from the electronic medical record databases of secondary- and tertiary-care hospitals. The medication profiles of patients were assessed to examine whether they were prescribed any PIMHF after an HF diagnosis. For PIMHF detection, the HF-specific criteria, including 2014 St Vincent criteria, 2019 Beers criteria, and 2021 Thailand criteria were applied. The prevalence of PIMHF use was expressed as percentages. The associated factors were identified using a binary logistic regression analysis, expressed as the adjusted odds ratio (aOR) and 95% confidence interval (95% CI).

RESULTS A total of 2,639 patients were included in the study. Thirty-two PIMHF were found to have been prescribed to these patients. The prevalence of PIMHF use identified by the ST Vincent criteria, the Beers criteria, the Thailand criteria, and the three combined criteria was 23.76%, 19.67%, 21.18%, and 25.16%, respectively. The factors associated with PIMHF use were secondary-care hospital (aOR = 1.54, 95% CI: 1.26–1.87), HF with preserved ejection fraction (HFpEF) (aOR = 1.81, 95% CI: 1.38–2.38), hypertension (HTN) (aOR = 1.24, 95% CI: 1.02–1.51), diabetes mellitus (DM) (aOR = 1.39, 95% CI: 1.10–1.75), chronic pulmonary diseases (CPD) (aOR = 2.09, 95% CI: 1.56–2.80), and connective tissue diseases (CTD) (aOR = 5.10, 95% CI: 2.20–11.83).

CONCLUSIONS PIMHF are commonly used in Thai older HF patients. The factors associated with PIMHF use identified in this study include secondary-care hospital, HFpEF, HTN, DM, CPD, and CTD.

Heart failure (HF) is a major health problem worldwide. The prevalence of HF in Americans aged ≥ 20 years rose from 5.7 (2009–2012) to 6.2 (2013–2016) million, with the incidence of HF in persons aged ≥ 55 years being a million in 2014.^[1] The 2019 public health statistics reported that heart diseases is one of the leading causes of death in Thais, with a mortality rate equaling 11.6 per 100,000 population.^[2] Adverse clinical outcomes have been reported in Thai HF patients, with rates of early readmission from all causes and in-hospital mortality of 14.07%^[3] and 5.5%,^[4] respectively.

HF is commonly found in older adults^[5] and has been reported to be the primary cause of rehospitalization in older HF patients.^[6] Several comorbidities, which might be cardiovascular (CV) or non-CV,

are often accompanied with HF. Van Deursen, *et al.* reported that 74% and 43% of older HF patients had ≥ 1 and ≥ 2 comorbidities, respectively.^[7] The frequently reported non-CV comorbidities were chronic kidney disease (CKD), anemia, diabetes, stroke, asthma and chronic obstructive pulmonary disease (COPD), and cancer.^[7,8]

Comorbidities lead to a requirement of prescription of multiple medications. Unlu, *et al.*^[9] revealed that 84% and 95% of older patients hospitalized for HF received ≥ 5 medications (polypharmacy) at admission and at discharge, respectively. Moreover, 42% and 55% of them were prescribed ≥ 10 medications (hyperpolypharmacy) at admission and at discharge, respectively.^[9] The similar findings were reported by recent studies. In a study by Dunlay, *et al.*,^[10]

the median (interquartile range) number of medications prescribed to older HF patients residing in one community was 11 (8, 17). Kennel, *et al.*^[11] found that the mean total number of prescribed medications was 7.2 ± 3.7 , and the mean number of non-CV medications was greater than that of CV medications (3.4 ± 2.7 vs. 2.1 ± 1.3). Apart from the medications to use with caution in older adults, medications that may exacerbate HF, which are called potentially inappropriate medications for patients with HF (PIMHF), should also be avoided in older HF patients.

Recently, the explicit criteria for PIMHF detection, including the 2014 ST Vincent criteria,^[12] 2019 Beers criteria,^[13] and 2021 Thailand criteria^[14] have been developed to use as an assessment tool for a medication review in HF patients. However, there is inconsistency among the criteria in terms of the number of medications and the medication names listed for each criterion, resulting in the prevalence being varied. Approximately 15% of HF outpatients received at least one PIMHF identified by the St Vincent criteria.^[12] Based on the 2015 Beers criteria, 80% of older HF patients received at least one PIM (PIMs for most older adults) with a mean of 1.6 ± 1.3 PIMs per one patient.^[15] PIMHF identified only from the Thailand criteria was found to be prescribed to 45.16% and 33.07% of HF patients of all ages at a secondary- and a tertiary-care hospital, respectively.^[16]

In older HF patients, both potentially inappropriate medications for older adults (PIMs) and PIMHF should be avoided. The prevalence of PIMs use in older HF patients was previously reported, whereas no report on the prevalence of PIMHF use in older HF patients was found, especially when identified by the existing HF-specific criteria. Additionally, such a report is required because Thai older HF patients normally receive care from general practitioners (GPs) rather than from cardiologists,^[17] and not all older HF patients receive a thorough review of medication use in real clinical practice, consequently leading to a high risk of PIMHF use. Thus, the present study can extend the scientific knowledge regarding the use of PIMHF in older HF patients in clinical practice. The purposes of the present study were to determine the prevalence of PIMHF use identified by HF-specific criteria and to identify the factors associated with PIMHF use in Thai older HF patients.

METHODS

Study Design and Setting

This study was a cross-sectional analytical survey using data on older HF patients retrieved from the electronic medical record (EMR) database of two public hospitals, including one secondary-care hospital (a 231-bed hospital) in Phayao Province and one tertiary-care hospital (an 800-bed hospital) in Lam-pang Province. The secondary-care hospital served as a referral center for the patients from the five districts, including the district where the hospital is located and the four nearby districts. The tertiary-care hospital served as an academic and referral center in the upper northern region of Thailand. At the time of the study, one and six cardiologists were available in a secondary- and a tertiary-care hospital, respectively. Although the HF clinic was carried out in both hospitals, only complex patients were chosen to attend the HF clinic. Data retrieval from the EMR databases was performed by the programmer of the hospital.

Both study hospitals were chosen because they provided complete data on the prescription of medications, including both medications on the hospital drug list and sample medications (pregabalin and mefenamic acid). The tertiary-care hospital is also a cancer center, so the prescription of anticancer drugs (one PIMHF) could be assessed. Furthermore, the medications available at the two study hospitals were different, i.e., terbutaline tablets and dexamethasone tablets were available only at the secondary- and the tertiary-care hospitals, respectively. When the two study hospitals were combined, 50 of 64 PIMHF, including 3 only from the secondary-care hospital, 24 only from the tertiary-care hospital, and 23 from both were assessed, yielding 78.13% coverage of PIMHF.

All data used in this study were obtained from our previous study (which aimed to determine the prevalence of PIMHF use identified only by the Thailand criteria in Thai HF patients of all ages) and were not related to patient identification.^[16] The same dataset provided sufficient data for use in the present study. The study protocol was reviewed as an exempt study and certified by the Human Ethics Committee of the University of Phayao (study code: UP-HEC 1.1/047/64, date of exemption: January 17, 2022) prior to data collection.



Study Patients

All patients aged ≥ 60 years (considered 'older person' Thais)^[18] diagnosed with HF visiting the study hospitals between January 1, 2017 and December 31, 2019 were included. The patients were identified as having HF using the following International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I43.0, I43.1, I43.2, I43.8, I50, I50.0, I50.1, I50.9, and P29.0.^[19] The patients who had no history of prescription during the study period were excluded from the study.

Procedure

All patient and medical data were obtained from the EMR databases, including demographics, i.e., gender, age, and age groups (60-74 and ≥ 75 years);^[17] clinical data including the type of HF classified by ejection fraction (EF, %), including heart failure with reduced ejection fraction (HFrEF, EF $< 40\%$), HF with mid-range EF (HFmrEF, EF = 41%-49%), and HF with preserved EF (HFpEF, EF $\geq 50\%$),^[20] CV and non-CV comorbidities, number of CV and non-CV comorbidities, comorbidities, number of comorbidities, and the comorbidity score which was calculated for individual patients using the Charlson Comorbidity Index (CCI)^[21] together with the ICD-10 coding algorithm for defining comorbidities.^[22]

The study medications comprised medications for HF treatment, including diuretics, beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), calcium channel blockers (CCB), nitrates, mineralocorticoid receptor antagonists (MRA), hydralazine, digoxin, ivabradine, and angiotensin receptor blocker/nepri-lysin inhibitors (ARNI)^[23,24] as well as the PIMHF gathered from HF-specific criteria. All study medications were identified using the medication codes of each study hospital. To ensure that the medications being assessed were considered to be PIMHF, an index date (the date when an HF diagnosis was first recorded on the database in 2017-2019) was assigned to each patient, and the medications prescribed from the index date until December 31, 2019 were assessed for PIMHF detection.

Criteria for PIMHF Detection

The three sets of HF-specific criteria applied in

this study included the 2014 St Vincent criteria,^[12] 2019 Beers criteria (only the category of drug-HF interactions),^[13] and 2021 Thailand criteria.^[14] The Beers criteria were developed for older adults, whereas the others were developed specifically for HF patients of all ages. All the criteria are related to HF-drug interactions (i.e., they include medications that may exacerbate HF) and are considered to be drug-oriented explicit criteria requiring no or little clinical information to be applied.^[25] The St Vincent criteria contain 11 medications/medication classes, the Beers criteria contain 6 medication/medication classes, whereas the Thailand criteria contain 47 medications on the National List of Essential Medicines (NLEM), which is the reason why mefenamic acid, loxoprofen, ketorolac, meloxicam, and parecoxib are not listed on the Thailand criteria.

In total, there were 64 PIMHF from the combined three criteria (34, 22, and 47 PIMHF from the ST Vincent, the Beers, and the Thailand criteria, respectively). All PIMHF are for all HF types, except for non-dihydropyridine (non-DHP) CCBs, which are PIMHF only for HFrEF. Sildenafil was identified as a PIMHF only for nitrate users. Metformin was identified as a PIMHF when used in HF patients with poor renal function (eGFR < 30 mL/min per 1.73 m²). As no eGFR was recorded on the databases, renal function was assessed using the following ICD-10 codes; N18.4 for CKD stage 4 (eGFR = 15-29 mL/min per 1.73 m²) and N18.5 for CKD stage 5 (eGFR < 15 mL/min per 1.73 m²).^[26] The medicinal formulations with high sodium content were reviewed and gathered from the recommendation by the American Heart Association (AHA).^[27]

Statistical Analysis

Normally distributed continuous variables were expressed as mean \pm SD, and comparisons between the two study hospitals were performed using independent sample *t*-tests. Non-normally distributed continuous variables were expressed as median and interquartile range (Q₁, Q₃), and comparisons between the two hospitals were performed using the Mann-Whitney *U* test. Categorical variables were expressed as frequencies and percentages, and comparisons between the two study hospitals were performed using the chi-squared test or Fisher's exact test as appropriate.



The prevalence of overall use and each PIMHF use was calculated by dividing the number of patients prescribed any PIMHF by the total number of the patients and expressed as percentages for each and all of the criteria. The number of times a PIMHF was prescribed is expressed as median and interquartile range (Q_1 , Q_3) for all PIMHF.

Data from the two study hospitals were pooled for the identification of the factors associated with PIMHF use. A binary logistic regression analysis was performed to calculate crude odds ratios (crude OR), adjusted odds ratios (aOR), and 95% confidence intervals (95% CI). In the univariate analysis, factors with a P -value less than 0.05 were incorporated into an adjustment analysis. To diagnose multicollinearity (two independent variables are highly correlated), the variance inflation factors (VIF) was calculated for each factor. Factors with $VIF \geq 10$ were excluded from the model.^[28] For the selection of the associated factors, a backward elimination method (the factor with least significance was discarded at each step) was used until all the remaining factors in the model had a P -value less than 0.05. All statistical analyses were performed using STATA release 14.0. All hypothesis tests were two-tailed, with P -values less than 0.05 being considered significant.

RESULTS

Patient Characteristics

The process of patient recruitment is shown in Figure 1. From the EMR databases, a total of 2709 older HF patients were initially included. Seventy patients were excluded due to a lack of history of prescription. Thus, 2639 eligible patients were included in the study.

The characteristics of the study patients are shown in Table 1. The patients were mostly female (54.98%) and had the average age of 73.71 ± 8.61 years. Of the patients with known EF (62.52%), HFpEF was the most common form, followed by HFrEF and HFm-rEF. Most of the patients (70.37%) had at least one comorbidity with the median number of comorbidities being 1 (0, 2). 60.59% of the patients had CV comorbidities, hypertension being most prevalent, and 47.44% had non-CV comorbidities, renal failure being most prevalent. For HF medications, diuretics was the most prescribed, followed by BB and CCB. A statistically significant difference in some characteristics was observed between the two study hospitals.

Prevalence of PIMHF Use

The prevalence of PIMHF use is summarized in Table 2. Thirty-two of 50 PIMHF assessed were found to have been prescribed to the patients. For the combined criteria, any PIMHF was found to have been prescribed to 664 (25.16%) patients, with the mean number of PIMHF being 1.31 ± 0.68 items per patient and the median number of times PIMHF prescribed being 2 (1, 6) times. For the individual criterion, the prevalence of PIMHF use according to the St Vincent criteria, the Beers criteria, and the Thailand criteria was 23.76%, 19.67%, and 21.18%, respectively. A higher prevalence of PIMHF use was found in the secondary-care hospital than in the tertiary-care hospital.

For distribution of the 32 PIMHF, oral prednisolone (11.94%) was the most prescribed, followed by metronidazole injection (3.71%), pioglitazone (3.56%), naproxen (2.80%), and azithromycin injection (1.86%). Only two and one patients with HFrEF

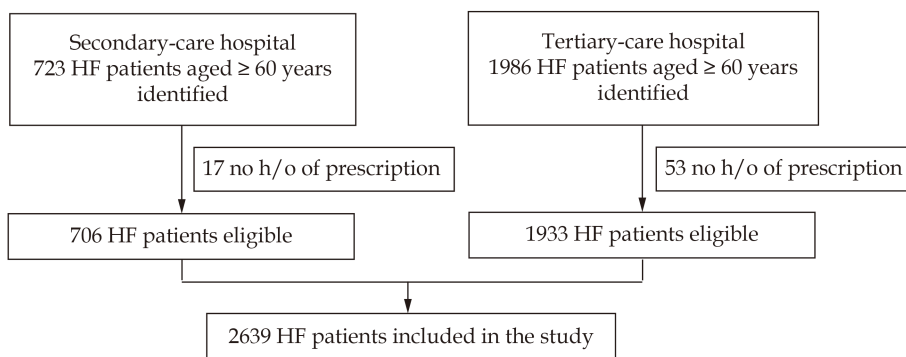


Figure 1 The process of patient recruitment. HF: heart failure.

Table 1 Characteristics of the study patients.

Characteristics	Total patients (n = 2,639)	Secondary-care hospital (n = 706)	Tertiary-care hospital (n = 1,933)	P-value
Demographics				
Female	1,451 (54.98%)	411 (58.22%)	1,040 (53.80%)	0.044
Age				
60-74 yrs	1,496 (56.69%)	376 (53.26%)	1,120 (57.94%)	0.032
≥ 75 yrs	1,143 (43.31%)	330 (46.74%)	813 (42.06%)	
Mean age, yrs	73.71 ± 8.61	74.44 ± 8.21	73.44 ± 8.74	0.009
Clinical characteristics				
Types of HF				
HFrEF	484 (18.34%)	89 (12.61%)	395 (20.43%)	< 0.001
HFmrEF	274 (10.38%)	45 (6.37%)	229 (11.85%)	
HFpEF	892 (33.80%)	241 (34.14%)	651 (33.68%)	
Unknown EF	989 (37.48%)	331 (46.88%)	658 (34.04%)	
CV comorbidities				
Hypertension	1,057 (40.05%)	338 (47.88%)	719 (37.20%)	< 0.001
Ischemic heart diseases	546 (20.69%)	115 (16.29%)	431 (22.30%)	0.001
Atrial fibrillation	510 (19.33%)	149 (21.10%)	361 (18.68%)	0.162
Cerebrovascular diseases	76 (2.88%)	27 (3.82%)	49 (2.53%)	0.080
Peripheral vascular diseases	36 (1.36%)	6 (0.85%)	30 (1.55%)	0.169
Number of CV comorbidities	1 (0, 1)	1 (0, 1)	1 (0, 1)	0.008
Non-CV comorbidities				
Renal failure	662 (25.09%)	287 (40.65%)	375 (19.40%)	< 0.001
Diabetes mellitus	513 (19.44%)	131 (18.56%)	382 (19.76%)	0.488
Chronic pulmonary diseases	219 (8.30%)	84 (11.90%)	135 (6.98%)	< 0.001
Dyslipidemia	73 (2.77%)	43 (6.09%)	30 (1.55%)	< 0.001
Prostatic hyperplasia	54 (2.05%)	19 (2.69%)	35 (1.81%)	0.157
Cancer	44 (1.67%)	13 (1.84%)	31 (1.60%)	0.673
Liver disease	36 (1.36%)	22 (3.12%)	14 (0.72%)	< 0.001
Osteoarthritis	31 (1.17%)	17 (2.41%)	14 (0.72%)	< 0.001
Connective tissue diseases	24 (0.91%)	5 (0.71%)	19 (0.98%)	0.510
Peptic ulcer	8 (0.30%)	2 (0.28%)	6 (0.31%)	0.911
Dementia	7 (0.27%)	0 (0.00%)	7 (0.36%)	0.109
AIDS	4 (0.15%)	1 (0.14%)	3 (0.16%)	0.937
Number of non-CV comorbidities	0 (0, 1)	1 (0, 1)	0 (0, 1)	< 0.001
Comorbidities	1,857 (70.37%)	582 (82.44%)	1,275 (65.96%)	< 0.001
Number of comorbidities	1 (0, 2)	2 (1, 3)	1 (0, 2)	< 0.001
Comorbidity score ≥ 2	1,242 (47.06%)	422 (59.77%)	820 (42.42%)	< 0.001
HF medications				
Diuretic	2,305 (87.34%)	631 (89.38%)	1,674 (86.60%)	0.058
BB	1,135 (43.01%)	275 (38.95%)	860 (44.49%)	0.011
CCB	943 (35.73%)	314 (44.48%)	629 (32.54%)	< 0.001



Continued

Characteristics	Total patients (n = 2,639)	Secondary-care hospital (n = 706)	Tertiary-care hospital (n = 1,933)	P-value
MRA	902 (34.18%)	201 (28.47%)	701 (36.26%)	< 0.001
Nitrate	810 (30.69%)	94 (13.31%)	716 (37.04%)	< 0.001
ACEI	766 (29.03%)	199 (28.19%)	567 (29.33%)	0.566
ARB	649 (24.59%)	107 (15.16%)	542 (28.04%)	< 0.001
Hydralazine	445 (16.86%)	91 (12.89%)	354 (18.31%)	0.001
Digoxin	246 (9.32%)	98 (13.88%)	148 (7.66%)	< 0.001
Ivabradine	14 (0.53%)	0	14 (0.72%)	0.023
ARNI	4 (0.15%)	0	4 (0.21%)	0.226

Data are presented as mean \pm SD or *n* (%). The number of CV co-morbidities, non-CV co-morbidities and co-morbidities are expressed as median and interquartile range (Q₁, Q₃). Categorical variables are expressed as frequencies and percentages. The *P*-value is for the comparison between the two study hospitals. ACEI: angiotensin-converting enzyme inhibitors; AIDS: acquired immune deficiency syndrome; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor blocker/neprilysin inhibitors; BB: beta-blockers; CCB: calcium channel blockers; CV: cardiovascular; HF: heart failure; MRA: mineralocorticoid receptor antagonists; PIMHF: potentially inappropriate medications for patients with heart failure.

Table 2 Summary of PIMHF from the three sets of HF-specific criteria.

PIMHF items	HF-specific criteria			Total patients <i>n</i> (%)	Number of times PIMHF prescribed Median (Q1, Q3)	Secondary-care hospital <i>n</i> (%)	Tertiary-care hospital <i>n</i> (%)
	St Vincent criteria	Beers criteria	Thailand criteria				
Prescribed with any PIMHF							
Combined three criteria				664 (25.16%)	2 (1, 6)	226 (32.01%)	438 (22.66%)
St Vincent criteria				627 (23.76%)	2 (1, 5)	219 (31.02%)	408 (21.11%)
Beers criteria				519 (19.67%)	2 (1, 5)	185 (26.20%)	334 (17.28%)
Thailand criteria				559 (21.18%)	2 (1, 6)	197 (27.90%)	362 (18.73%)
50 PIMHF assessed [†]							
Prednisolone, oral	•	•	•	315 (11.94%)	2 (1, 5)	126 (17.85%)	189 (9.78%)
Metronidazole, injection	•			98 (3.71%)	1.5 (1, 4)	46 (6.52%)	52 (2.69%)
Pioglitazone	•	•	•	94 (3.56%)	4 (1, 8)	32 (4.53%)	62 (3.21%)
Naproxen	•	•	•	74 (2.80%)	1 (1, 2)	26 (3.68%)	48 (2.48%)
Azithromycin, injection	•			49 (1.86%)	1 (1, 1)	N/A	49 (2.53)
Diclofenac	•	•	•	47 (1.78%)	1 (1, 2)	10 (1.42%)	37 (1.91%)
Ibuprofen	•	•	•	27 (1.02%)	1 (1, 1)	13 (1.84%)	14 (0.72%)
Prazosin			•	22 (0.83%)	4 (1, 13)	8 (1.13%)	14 (0.72%)
Celecoxib	•	•	•	18 (0.68%)	1 (1, 2)	6 (0.85%)	12 (0.62%)
Methotrexate			•	14 (0.53%)	4 (1, 7)	2 (0.28%)	12 (0.62%)
Clozapine			•	14 (0.53%)	1.5 (1, 4)	1 (0.14%)	13 (0.67%)
Salbutamol, oral	•		•	12 (0.45%)	1 (1, 1)	12 (1.70%)	0
Cyclophosphamide			•	12 (0.45%)	3.5 (1, 6.5)	1 (0.14%)	11 (0.57%)
Itraconazole	•			11 (0.42%)	2 (1, 3)	6 (0.85%)	5 (0.26%)
Pregabalin	•			11 (0.42%)	2 (1, 3)	2 (0.28%)	9 (0.47%)
Pseudoephedrine	•		•	9 (0.34%)	1 (1, 2)	2 (0.28%)	7 (0.36%)
Meloxicam	•	•		8 (0.30%)	1 (1, 2.5)	6 (0.85%)	2 (0.10%)
Etoricoxib	•	•	•	7 (0.27%)	1 (1, 2)	N/A	7 (0.36%)
Parecoxib	•	•		7 (0.27%)	1 (1, 1)	N/A	7 (0.36%)
Dexamethasone, oral	•	•	•	6 (0.23%)	1.5 (1, 2)	N/A	6 (0.31%)



Continued

PIMHF items	HF-specific criteria			Total patients n (%)	Number of times PIMHF prescribed Median (Q1, Q3)	Secondary-care hospital n (%)	Tertiary-care hospital n (%)
	St Vincent criteria	Beers criteria	Thailand criteria				
Cilostazol		•		5 (0.19%)	2 (1, 2)	N/A	5 (0.26%)
Piroxicam	•	•	•	2 (0.08%)	1 (1, 1)	N/A	2 (0.10%)
Diltiazem slow release (in HFrEF)	•	•	•	2 (0.08%)	4 (2, 6)	N/A	2 (0.10)
Indomethacin	•	•	•	1 (0.04%)	1 (1, 1)	0	1 (0.05%)
Verapamil (in HFrEF)	•	•	•	1 (0.04%)	1 (1, 1)	0	1 (0.05%)
Procaterol	•			1 (0.04%)	11 (11, 11)	1 (0.14%)	N/A
Melphalan			•	1 (0.04%)	1 (1, 1)	N/A	1 (0.05%)
Fluorouracil			•	1 (0.04%)	2 (2, 2)	N/A	1 (0.05%)
Paclitaxel			•	1 (0.04%)	2 (2, 2)	N/A	1 (0.05%)
Docetaxel			•	1 (0.04%)	1 (1, 1)	N/A	1 (0.05%)
Trastuzumab			•	1 (0.04%)	1 (1, 1)	N/A	1 (0.05%)
Ergotamine plus caffeine			•	1 (0.04%)	1 (1, 1)	0	1 (0.05%)
Mefenamic	•	•		0	-	0	0
Loxoprofen	•	•		0	-	N/A	0
Ketorolac	•	•		0	-	N/A	0
Diltiazem immediate release (in HFrEF)	•	•	•	0	-	0	N/A
Terbutaline, oral	•		•	0	-	0	N/A
Chlorambucil			•	0	-	N/A	0
Ifosfamide			•	0	-	N/A	0
Mitomycin			•	0	-	0	0
Dactinomycin			•	0	-	N/A	0
Doxorubicin			•	0	-	N/A	0
Idarubicin			•	0	-	N/A	0
Capecitabine			•	0	-	N/A	0
Mercaptopurine			•	0	-	N/A	0
Bleomycin			•	0	-	N/A	0
Lithium			•	0	-	0	0
Sildenafil (when used with nitrates)			•	0	-	N/A	0
Metformin (in poor renal function)	•			0	-	0	0
Piperacillin sodium + sulbactam sodium, injection	•			0	-	N/A	0
14 PIMHF unassessed							
Ampicillin sodium + sulbactam sodium, injection	•			N/A	N/A	N/A	N/A
Busulfan			•	N/A	N/A	N/A	N/A
Carmustine			•	N/A	N/A	N/A	N/A
Clonidine			•	N/A	N/A	N/A	N/A
Dronedarone		•	•	N/A	N/A	N/A	N/A
Flecainide			•	N/A	N/A	N/A	N/A
Fludrocortisone, oral	•	•	•	N/A	N/A	N/A	N/A



Continued

PIMHF items	HF-specific criteria			Total patients n (%)	Number of times PIMHF prescribed Median (Q1, Q3)	Secondary-care hospital n (%)	Tertiary-care hospital n (%)
	St Vincent criteria	Beers criteria	Thailand criteria				
Hydrocortisone, oral	•	•	•	N/A	N/A	N/A	N/A
Mitoxantrone			•	N/A	N/A	N/A	N/A
Omeprazole/sodium bicarbonate	•			N/A	N/A	N/A	N/A
Polyethylene glycol powder for solution	•			N/A	N/A	N/A	N/A
Pramipexole			•	N/A	N/A	N/A	N/A
Procarbazine			•	N/A	N/A	N/A	N/A
Ranitidine, pre-mixed bag sodium phosphates solution	•			N/A	N/A	N/A	N/A
Total	34	22	47			26	47

*Listed by frequency in descending order. The medicinal formulations with a high sodium content (sodium content per unit) include metronidazole injection (790 mg/500 mg vial), azithromycin injection (114 mg/500 mg vial), ampicillin sodium + sulbactam sodium injection (115 mg /1.5 g vial), omeprazole/sodium bicarbonate (304 mg/capsule and 406 mg /packet), polyethylene glycol powder for solution (1.46 g/1 L), and ranitidine, pre-mixed bag sodium phosphate solution (225 mg/50 mg vial). CV: cardiovascular; HFREF: heart failure with reduced ejection fraction; N/A: not available; PIMHF: inappropriate medications for patients with heart failure.

were prescribed diltiazem slow release and verapamil, respectively. Although there were 67 patients diagnosed with CKD stage 4 and 5 and DM, none of them received metformin. The top three PIMHF, including oral prednisolone, metronidazole injection,

and pioglitazone, appeared similar between the two study hospitals.

The most prescribed classes of PIMHF are shown in Figure 2. In the two hospitals combined, oral corticosteroids (12.16%) were the most prescribed, fol-

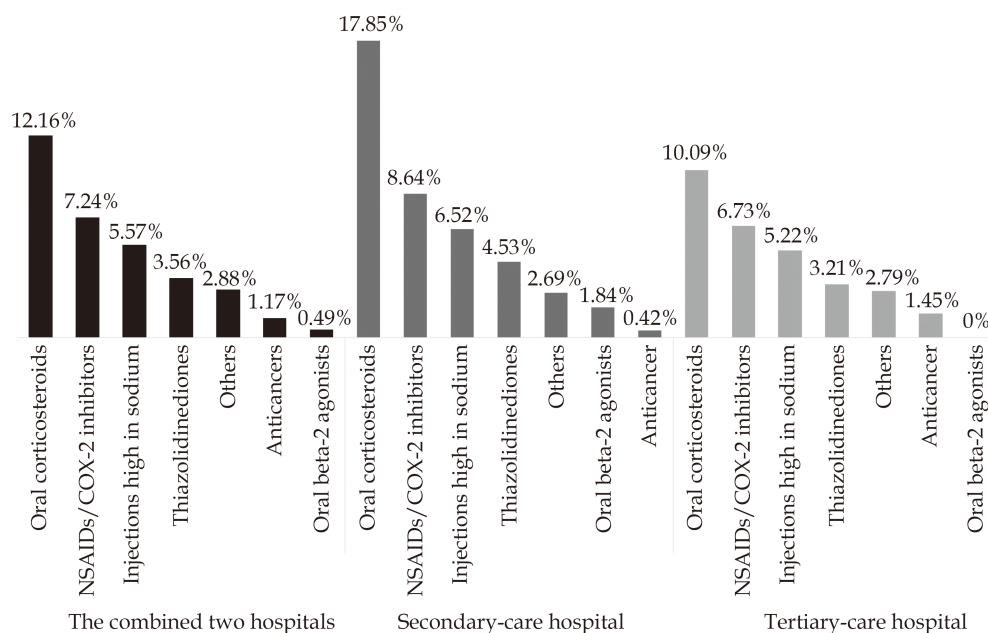


Figure 2 The most prescribed classes of PIMHF according to the study hospitals. Oral corticosteroids include prednisolone and dexamethasone. NSAIDs/COX-2 inhibitors include diclofenac, ibuprofen, piroxicam, indomethacin, naproxen, meloxicam, celecoxib, etoricoxib, and parecoxib. Injections with high sodium content include metronidazole and azithromycin. Thiazolidinediones include pioglitazone. Oral beta-2 agonists include salbutamol and procaterol. Anticancer drugs include cyclophosphamide, melphalan, fluorouracil, paclitaxel, docetaxel, trastuzumab, and methotrexate. Other medications include Prazosin, Clozapine, Itraconazole, pregabalin, pseudoephedrine, cilostazol, ergotamine plus caffeine, diltiazem slow release, and verapamil. PIMHF: inappropriate medications for patients with heart failure.



lowed by NSAIDs/COX-2 inhibitors (7.24%) and injections with a high sodium content (5.57%). Both of the hospitals had a similarity of the most prescribed classes of PIMHF except for oral beta-2 agonists and anticancer drugs, which were more prescribed in the secondary-care hospital and in the tertiary-care hospital, respectively.

Factors Associated with PIMHF Use

The factors found to be associated with PIMHF

use obtained from the univariate analysis are shown in Table 3. In the multivariate analysis, the factors significantly associated with PIMHF use included secondary-care hospital, HFpEF, hypertension (HTN), diabetes mellitus (DM), chronic pulmonary diseases (CPD), and connective tissue diseases (CTD). Compared with the referent group of patients from the tertiary-care hospital, those from the secondary-care hospital had an odds ratio of 1.54 (95% CI: 1.26–1.87). Compared with the referent group of patients

Table 3 The univariate analysis.

Potential factors	Crude ORs (95% CIs)	P-values
Secondary-care hospital	1.61 (1.33–1.94)	< 0.001*
Female	1.02 (0.86–1.22)	0.793
Age ≥ 75 yrs (ref. = age 60–74 yrs)	1.15 (0.97–1.38)	0.115
HFmrEF (ref. = HFrEF)	1.45 (1.01–2.07)	0.043*
HFpEF (ref. = HFrEF)	1.92 (1.47–2.52)	< 0.001*
Unknown EF (ref. = HFrEF)	1.36 (1.03–1.78)	0.028*
CV comorbidities	1.08 (0.90–1.29)	0.426
Hypertension	1.44 (1.21–1.72)	< 0.001*
Ischemic heart diseases	0.88 (0.70–1.10)	0.251
Atrial fibrillation	0.83 (0.66–1.04)	0.104
Cerebrovascular diseases	0.79 (0.45–1.38)	0.403
Peripheral vascular diseases	0.99 (0.46–2.12)	0.982
Number of CV comorbidities	1.05 (0.94–1.17)	0.371
Non-CV comorbidities	1.69 (1.42–2.02)	< 0.001*
Renal failure	1.20 (0.98–1.46)	0.071
Diabetes mellitus	1.48 (1.19–1.82)	< 0.001*
Chronic pulmonary diseases	2.11 (1.58–2.80)	< 0.001*
Dyslipidemia	0.97 (0.57–1.67)	0.920
Prostatic hyperplasia	1.63 (0.93–2.87)	0.089
Cancer	0.99 (0.50–1.97)	0.980
Liver disease	1.31 (0.64–2.69)	0.454
Osteoarthritis	0.87 (0.37–2.02)	0.739
Connective tissue diseases	5.05 (2.20–11.59)	< 0.001*
Peptic ulcer	0.42 (0.05–3.45)	0.423
Dementia	0.49 (0.06–4.12)	0.515
AIDS	2.98 (0.42–21.20)	0.275
Number of non-CV comorbidities	1.37 (1.23–1.53)	< 0.001*
Comorbidities	1.22 (1.00–1.48)	0.052
Number of comorbidities	1.15 (1.07–1.23)	< 0.001*
Comorbidity score ≥ 2	1.70 (1.42–2.03)	< 0.001*

*Factors with *P*-values less than 0.05 were incorporated into a multivariate analysis. In the multicollinearity test, non-CV comorbidities, the number of non-CV comorbidities, and the number of comorbidities were excluded, with VIFs equal to 11.38, 10.62, and 11.51, respectively. AIDS: acquired immune deficiency syndrome; CV: cardiovascular; HFrEF: heart failure with reduced ejection fraction; VIFs: variance inflation factors.



with HF_rEF, those with HF_pEF had an odds ratio of 1.81 (95% CI: 1.38–2.38). Compared with the referent group of patients with no HTN, those with HTN had an odds ratio of 1.24 (95% CI: 1.02–1.51). Compared with the referent group of patients with no DM, those with DM had an odds ratio of 1.39 (95% CI: 1.10–1.75). Compared with the referent group of patients with no CPD, those with CPD had an odds ratio of 2.09 (95% CI: 1.56–2.80). Compared with the referent group of patients with no CTD, those with CTD had an odds ratio of 5.10 (95% CI: 2.20–11.83).

The association of PIMHF with chronic comorbidities commonly accompanying HF (as an indication for PIMHF) was observed as follows: DM with pioglitazone (OR = 13.06, 95% CI: 8.17–20.87), CPD (asthma and COPD) with oral corticosteroids (OR = 4.20, 95% CI: 3.08–5.74), CTD (rheumatoid arthritis, systemic lupus erythematosus) with NSAIDs/COX-2 inhibitors (OR = 3.38, 95% CI: 1.14–10.02), with oral corticosteroids (OR = 5.33, 95% CI: 2.35–12.10), and with methotrexate (OR = 108.63, 95% CI: 34.20–344.97), cancer with anticancer drugs (OR = 6.96, 95% CI: 2.03–23.86), prosthetic hyperplasia with prazosin (OR = 20.07, 95% CI: 7.53–53.52), and hypertension with prazosin (OR = 2.64, 95% CI: 1.10–6.32).

DISCUSSION

The prevalence of PIMHF use found in our study was 23.76%, 19.67%, 21.18%, and 25.16% when identified by the St Vincent criteria, the Beers criteria, the Thailand criteria, and the three combined criteria, respectively. The factors found to be associated with PIMHF use were secondary-care hospital, HF_pEF, and common comorbidities, including HTN, DM, CPD, and CTD.

When medications are used in older HF patients, two important factors to consider are their age and HF. With aging, potentially inappropriate medications (PIMs) suggested by the criteria like the Beers criteria should be deprescribed or avoided in older adults because of their association with an increased risk of adverse drug events.^[23] In this case, even diuretics (one of the HF medications) are considered PIM (diuretics may exacerbate or cause inappropriate antidiuretic hormone secretion or hyponatremia).^[13] Zahwe, *et al.*^[15] reported that diuretics (55.2%)

are the most commonly prescribed PIMs in older HF patients. Also, the prevalence of PIMs based on the 2015 Beers criteria was reported to be 80%, with the category of medications to use with caution in older patients being 61.6%.^[15] A more recent study revealed that the prevalence of PIMs from the 2019 Beers criteria was 61.1% at admission and 64.0% at discharge among older adults hospitalized for HF.^[29] For HF, PIMHF should also be avoided. In general HF patients, the prevalence of PIMHF use according to the St Vincent criteria and the Thailand criteria was reported to be 14.06%^[12] and 36.11%,^[16] respectively. Currently, there is no report on the prevalence of PIMHF use identified by the HF-specific criteria in older HF patients, so a comparison cannot be made.

The prevalence of PIMHF use varied among the three criteria. The prevalence appeared not to be related to the total number of PIMHF, but depended on which PIMHF was listed on each criterion. The highest prevalence was found when the St Vincent criteria were used because several PIMHF only from this criterion were found to have been often prescribed, including medicinal formulations with a high sodium content (metronidazole injection and azithromycin injection), itraconazole, pregabalin, and procaterol. Although the Thailand criteria propose up to 47 PIMHF, several PIMHF, including anticancer drugs, ergotamine plus caffeine, lithium, and sildenafil in nitrate users were found to have been prescribed to only a few or no patients. All of the PIMHF from the Beers criteria, except for cilostazol, were also listed in the aforementioned criteria, resulting in the lowest prevalence. A higher prevalence of PIMHF use (for all the criteria) was observed in the secondary-care hospital than in the tertiary-care hospital. This might be because the quality of care older HF patients receive might have been better in the tertiary-care hospital.

For PIMHF listed on all the criteria, oral corticosteroids were the most prescribed, consistent with previous studies indicating that oral corticosteroids are frequently used in general HF patients.^[12,16] NSAIDs/COX-2 inhibitors were the second most prescribed, consistent with a previous study.^[16] This PIMHF class can elevate blood pressure and promote fluid retention by reducing the synthesis of renal prostaglandins, PGE₂, and prostacyclin.^[30] The association of



the use of NSAIDs/COX-2 inhibitors with the occurrence of HF and the risk of HF hospitalization has been reported in previous studies.^[30,31] Nevertheless, one recent study revealed that this medication class is still widely used as analgesics in older patients with cardiovascular diseases.^[32] Pioglitazone (thiazolidinediones) came in third, consistent with a previous study.^[16] According to the Thailand HF practice guideline, thiazolidinediones are not recommended in HF patients with DM due to the increased risk of worsening heart failure and hospitalization. Metformin and SGLT-2 inhibitors are safer alternatives.^[33] Non-DHP CCBs were found to have been slightly prescribed in patients with HFpEF. This might be because non-DHP CCBs are often avoided in older patients who are prone to the negative inotropic effect, as suggested by a study of Griffiths, *et al.*^[34] showing that non-DHP CCBs can contribute to drug-related bradycardia among hospitalized older adults. For PIMHF listed on either of the criteria, medicinal formulations with a high sodium content (on the St Vincent criteria) were found to be frequently used. In fact, the active medication in these formulations have no negative effect on HF, which is the reason why this medication class is not included in the other criteria. A restriction of sodium intake not exceeding 2 g/day is recommended for Thai HF patients.^[35] Our findings suggest that metronidazole injection which contains a very high sodium level (790 mg per a vial) and is frequently used in clinical practice, so sodium daily intake should be closely monitored. Moreover, 17.5% of the HF patients with renal dysfunction received metformin in a study by Bermingham, *et al.*,^[12] whereas none of our patient received metformin. In Thailand, a project promoting the rational use of medications has been implemented in hospitals, including the study hospitals. Avoiding metformin in cases of poor renal function is proposed as one of the indicators of the project, resulting in the prevalence of metformin in renal dysfunction being zero.^[36] Cilostazol (on the Beers criteria) was prescribed in 5 patients. Prazosin, methotrexate, clozapine, ergotamine plus caffeine, and several anticancer drugs (on the Thailand criteria) were also prescribed. Thus, we suggest that all the HF-specific criteria should be collectively used to identify all possible PIMHF.

In this study, the secondary-care hospital, HFpEF,

and some common comorbidities were identified as the factors associated with PIMHF use. The secondary-care hospital might have limited healthcare resources, e.g., cardiologists and healthcare personnel who care for HF patients and the availability of alternatives, leading to a higher probability of PIMHF use. In older HF patients, HFpEF was the most common form and was frequently accompanied of comorbidities, which might be an indication for PIMHF.^[37] Comorbidities were associated with overall and specific PIMHF use. CTD appeared to be the most influential factor, with an OR of 5.10, as it was associated with several PIMHF. This study extends a previous study by Zahwe, *et al.*,^[15] which reported that the number of medications, age \geq 85 years, CKD, and HF with New York Heart Association class III were the factors associated with more PIM use in older HF patients.

There were several strengths of our study. First, this study reported the prevalence of PIMHF use identified by the existing HF-specific criteria, using real data from a large older HF population. Second, the prescription of medications were all recorded on the EMR databases, so PIMHF not listed on the hospital drug list could be assessed. Third, of 64 PIMHF abstracted from the three criteria, up to 50 PIMHF were assessed. Lastly, each patient's medication profile was assessed after they had been diagnosed with HF, so the medication was definitely identified as a PIMHF.

There are some limitations to our study. First, only two hospitals were studied, which could not cover all 64 PIMHF, so the unavailable PIMHF that might be available in other hospitals have not been assessed in this study. Second, PIMHF was identified only by HF-specific, drug-oriented criteria, which might not consider other relevant clinical information. For example, the use of non-DHP CCBs with NYHA class III and IV HF is considered inappropriate based on the Screening Tool of Older Person's Prescriptions (STOPP) criteria.^[38] Third, each patient's medication profile was assessed from the index date until the end of 2019, so some patients had a short study period for medication assessment. Moreover, the patients might have received PIMHF from outside the hospital. In both cases, the prevalence of PIMHF use might have been higher than that reported in this study. Fourth, PIMHF might have been



prescribed without a clinical indication or prescribed for other conditions that were not included in this study (e.g., NSAIDs used for migraine or oral corticosteroids used for autoimmune diseases). Lastly, our findings should probably not be generalized to other settings with different available PIMHF and patterns of prescribing.

In conclusion, PIMHF use is common among Thai older HF patients. A careful review of medication use through effective approaches like comprehensive geriatric assessment or expert pharmacist review is required to deprescribe unnecessary PIMHF. The strategy should be focused primarily on patients in secondary-care hospitals and patients with HFpEF, HTN, DM, CPD, and CTD.

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