Associations of worsening renal function with loop diuretics in patients with heart failure with different ejection fraction categories

Marvin Owusu-Ayeman
Sun Yat-sen University First Affiliated Hospital
Xin He
Sun Yat-sen University First Affiliated Hospital
Weihao Liang
Sun Yat-sen University First Affiliated Hospital
Wengen Zhu
Sun Yat-sen University First Affiliated Hospital
Yuzhong Wu
Sun Yat-sen University First Affiliated Hospital
Ruicong Xue
Sun Yat-sen University First Affiliated Hospital
Zexuan Wu
Sun Yat-sen University First Affiliated Hospital
Bin Dong
Sun Yat-sen University First Affiliated Hospital
Yuanyuan Zhou
Sun Yat-sen University First Affiliated Hospital
Yugang Dong
Sun Yat-sen University First Affiliated Hospital
Fang-Fei Wei
Sun Yat-sen University First Affiliated Hospital
Chen Liu (✉ liuch75@mail.sysu.edu.cn)
The First Affiliated Hospital of Sun Yat-sen University; Key Laboratory on Assisted Circulation, Ministry of Health https://orcid.org/0000-0002-9818-0454

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Abstract

Background

Heart failure patients with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) have different sensitivity to plasma volume change after decongestion, but the possible differential effects of loop diuretics dosage on worsening renal function (WRF) in heart failure (HF) categories remain unclear.

Methods

In 972 patients with HFpEF and 427 patients with HFrEF, we assessed the risk of WRF with the average daily furosemide equivalent dose, using multivariable logistic regression. WRF was defined as an increase in serum creatinine levels of more than 26.5 mmol/L during hospitalization.

Results

In patients with HFpEF and HFrEF, between-group differences in average daily furosemide equivalent dose (18.9 mg/d vs. 26.8 mg/d) and the prevalence of WRF (25.3% vs. 14.3%) were significant ($p < 0.001$). In multivariable-adjusted analyses, a doubling of the average furosemide equivalent dose was associated with higher risk of WRF in all patients, patients with HFpEF and HFrEF, with odds ratios amounting to 1.42, 1.41 and 1.60 ($p \leq 0.022$), respectively. There was no interaction between heart failure categories and average furosemide equivalent dose ($p = 0.37$). The adjusted odds ratios of risk of WRF associated with intravenous furosemide were 1.26 (95% confidence interval [CI], 1.08–1.46; $p = 0.002$) in HFpEF but not significant in HFrEF($p = 0.099$).

Conclusions

The risk of WRF was associated with higher furosemide dosage in both HF subtypes. Our observations highlight that close monitoring is required to prevent further renal impairment in all HF patients while using loop diuretics.

Background

In Acute decompensated heart failure(ADHF), the use of diuretics for decongestion is inevitable and considered as one of the important treatment therapies in heart failure[1, 2]. Above 85% ADHF patients enrolled in the ADHERE registry received diuretic therapy[3]. Higher doses of loop diuretics improved symptoms, increased diuresis and reduced length of hospital stay in severe heart failure patients[4, 5]. However, aggressive diuretic usage led to worsening renal function (WRF) in ADHF patients[6–8].

Worsening renal function can be defined as increase in serum creatinine, usually > 26.5 mmol/L[9]. WRF is known to be associated with increased mortality amongst ADHF patients[10–12]. The mechanisms for WRF are not well-known and complex, but plasma volume reduction may play a vital role in WRF development[13]. Patients with HF with preserved (HFpEF) and reduced (HFrEF) ejection fraction have different sensitivity to changes in plasma volume and HFpEF are more likely to develop WRF due to the differences in the pathophysiology of these phenotypes[14]. Thus, patients with different HF subtypes may have different risks of developing WRF due to the treatment of diuretics. However, there was no study exploring the possible differential effects of loop diuretics dosage on WRF in HFpEF and HFrEF. In the present study, we examined the association of the risk of WRF with the daily dosage of loop diuretics in ADHF patients with HFpEF and HFrEF.

Methods

Study participants

This present study was a single-center retrospective observational study. Our study recruited 7,512 HF patients admitted at the First Affiliated Hospital of Sun Yat-Sen University between November 2013 and December 2017. The study protocol complies with the Helsinki Declaration and received was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University. The inclusion criteria: (i) patients were more than 18 years old; (ii) patients were diagnosed as ADHF; and (iii) use of diuretic treatment during hospitalization. Patients were diagnosed as ADHF if at least one symptom (edema, dyspnea, orthopnea, and abdominal distension), the presence of one sign (rales, elevated jugular venous pressure, cardiac murmur, enhanced apical beat, and peripheral edema), use of diuretic treatment and paroxysmal nocturnal dyspnea[15]. Two independent cardiologists adjudicated the diagnosis of ADHF. Finally, 1399 consecutive patients were included in this study (Fig. 1). Of these, 972 had HFpEF (EF ≥ 40%) and 427 had HFrEF (EF < 40%).

Diuretic dosage conversions

The dose of oral furosemide and other loop diuretics were converted into equivalents of furosemide infusion (20 mg torsemide = 40 mg intravenous furosemide = 80 mg oral furosemide)[16]. The daily average furosemide equivalent dose used during admission was calculated as the total furosemide dose from admission till discharge divided by the number of days of hospital stay.

Outcome

WRF is defined as an increase in serum creatinine levels of more than 0.3 mg/dL (> 26.5 mmol/L) according to the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure[9].

Statistical analysis

Data analysis was performed using SPSS 23.0 statistical software (IBM Corp, Armonk, NY, USA). Statistical significance was a 2-sided *p* value of 0.05 or less. Continuous and categorical variables were expressed as means ± SD and as number of participants (%), respectively. Means and proportions were compared using t-statistic, the χ2-statistic or Fisher exact test, respectively. The normality of all continuous variables was tested using the Kolmogorov–Smirnov test. We normalized the distribution of the daily average furosemide equivalent dose by a logarithmic transformation.

We determined differences in the prevalence of WRF across tertiles of the daily average furosemide equivalent dose in HFpEF and HFrEF. We computed odds ratio of having prevalent WRF associated with doubling of the daily average furosemide equivalent dose using logistic regression. In multivariable-adjusted analyses, we entered as covariables age, gender, systolic blood pressure(SBP), body mass index (BMI), diabetes mellitus, atrial fibrillation, sodium(Na), estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), use of statin, beta-blockers (BB), spironolactone, and angiotensin-converting enzyme inhibitors or angiotensin receptor blocker(ACEI/ARB). In a sensitivity analysis, patients were categorized according to the use of intravenous loop diuretics for the overall population, HFpEF, and HFrEF patients.

Results

Baseline characteristics

866 (61.9%) patients were men, 308 (22.0%) were smokers, 818 (58.5%) had hypertension and 533 (38.1%) diabetes mellitus. Age averaged (± SD) 68.3 ± 14.2 years, systolic and diastolic blood pressure 127.4 ± 23.9 mmHg and 75.0 ± 14.6 mmHg, respectively. Compared with patients with HFrEF, patients with HFpEF were older, had higher systolic blood pressure, higher prevalence of hypertension and atrial fibrillation ($p < 0.001$), whereas the opposite was true for heart rate, diastolic blood pressure, estimated glomerular filtration rate, NT-proBNP and the frequency of smoking ($p \leq 0.027$). Patients with HFpEF compared with those with HFrEF were more likely to take angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blockers, furosemide, spironolactone, aspirin and digoxin during hospitalization ($p \leq 0.018$).

Prevalence of WRF

The prevalence of WRF was higher in HFpEF than HFrEF. The prevalence of WRF increased across tertiles of the average diuretic dose in both HFpEF ($p < 0.001$; Fig. 2) and in HFrEF ($p = 0.073$; Fig. 2).

3.3 Association of the risk of WRF with loop diuretics

As shown in Table 2, the odds ratios (OR) expressing the crude risk of WRF associated with a doubling of the average diuretic dose were 1.39 (95% confidence interval [CI], 1.26–1.54; $p < 0.001$) in all patients, 1.55 (95% CI, 1.37–1.76; $p < 0.001$) in HFpEF patients and 1.22 (95% CI, 0.98–1.53; $p = 0.077$) in HFrEF patients. After adjusted for the confounders including age, gender, body mass index, systolic blood

pressure, diabetes mellitus, atrial fibrillation, sodium, estimated glomerular filtration rate, left ventricular EF, use of statin, beta-blockers, spironolactone, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (Table 2), the odds ratios were 1.42 in all patients (95% CI, 1.21–1.66; $p < 0.001$), 1.41 in HFpEF patients (95% CI, 1.20–1.68; $p < 0.001$) and 1.60 (95% CI, 1.07–2.38, $p = 0.022$) in HFrEF patients. However, there was no interaction between HF categories and average daily diuretic dosage ($p = 0.37$) in terms of the risk of WRF.

Table 1
shows the baseline characteristics of this study of the HF categories. Among all patients,

	HFpEF (*n* = 942)	HFrEF (*n* = 427)	*p* value
Age, y	70.9 ± 13.1	62.4 ± 14.7	< 0.001
Male, n (%)	542 (55.8)	324 (75.9)	< 0.001
Smoking, n (%)	193 (19.9)	115 (26.9)	0.003
Heart rate, bpm	84.2 ± 21.9	88.5 ± 18.4	< 0.001
Systolic blood pressure, mmHg	131.2 ± 24.4	118.9 ± 20.3	< 0.001
Diastolic blood pressure, mmHg	74.5 ± 14.9	76.2 ± 13.8	0.037
Body mass index, kg/m^2	23.7 ± 4.9	23.9 ± 5.1	0.382
Symptom			
Dyspnea, n (%)	574 (59.0)	331 (77.5)	< 0.001
Medical History			
Ischemic heart disease, n (%)	460 (47.3)	190 (44.5)	0.33
Diabetes mellitus, n (%)	373 (38.4)	160 (37.5)	0.75
Hypertension, n (%)	624 (64.2)	194 (45.4)	< 0.001
Atrial fibrillation, n (%)	365 (37.6)	78 (18.3)	< 0.001
Laboratory Data			
Hemoglobin, g/L	115.5 ± 24.4	131.9 ± 21.4	< 0.001
Sodium, mmol/L	138.5 ± 4.92	138.5 ± 4.74	0.98
eGFR, ml/min	64.4 ± 38.0	71.3 ± 31.4	< 0.001
NT-proBNP, pg/mL	3376.8 (1421.0-6712.7)	5231.2 (2658.9-9682.8)	< 0.001
Echocardiographic Parameter			
LVEF (%)	59.3 ± 11.2	29.6 ± 6.39	< 0.001
Treatment			

Abbreviations: *HFpEF* Heart Failure with Preserved Ejection Fraction; *HFrEF* Heart Failure with Reduced Ejection Fraction; *eGFR* indicates estimated glomerular filtration rate; eGFR was calculated using the Modification of Diet in Renal Disease equation; *ACEI* indicates angiotensin-converting enzyme inhibitor; *ARB* angiotensin receptor blocker; *LVEF* Left Ventricular Ejection Fraction. Data for categorical variables as number of patients *n* (%). The central tendency (spread) was represented by the arithmetic mean (SD) for normally distributed variables and by the geometric mean (interquartile range) for log-normally distributed variables.

	HFpEF (*n* = 942)	HFrEF (*n* = 427)	*p* value
ACEI/ARB, n (%)	730 (75.1)	358 (83.8)	< 0.001
Beta-blocker, n (%)	836 (86.0)	390 (91.3)	0.005
Furosemide tablet, n (%)	877 (90.2)	402 (94.2)	0.016
Furosemide infusion, n (%)	704 (72.4)	335 (78.4)	0.018
Average furosemide dose, mg/d	18.9 (11.7–33.3)	26.8 (15.0-42.5)	< 0.001
Spironolactone, n (%)	813 (83.6)	409 (95.8)	< 0.001
Amiodarone, n (%)	139 (14.3)	61 (14.3)	0.99
Statin, n (%)	734 (75.5)	314 (73.5)	0.43
Clopidogrel, n (%)	571 (58.7)	266 (62.3)	0.21
Aspirin, n (%)	456 (46.9)	242 (56.7)	0.001
Digoxin, n (%)	322 (33.1)	239 (56.0)	< 0.001

Abbreviations: *HFpEF* Heart Failure with Preserved Ejection Fraction; *HFrEF* Heart Failure with Reduced Ejection Fraction; *eGFR* indicates estimated glomerular filtration rate; eGFR was calculated using the Modification of Diet in Renal Disease equation; *ACEI* indicates angiotensin-converting enzyme inhibitor; *ARB* angiotensin receptor blocker; *LVEF* Left Ventricular Ejection Fraction. Data for categorical variables as number of patients *n* (%). The central tendency (spread) was represented by the arithmetic mean (SD) for normally distributed variables and by the geometric mean (interquartile range) for log-normally distributed variables.

Table 2
Risk of WRF in Relation to the Doubling of Average Daily Furosemide Equivalent Dose.

HF categories	UNADJUSTED		ADJUSTED		FULLY ADJUSTED	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
ALL	1.39 (1.26–1.54)	< 0.001	1.44 (1.28–1.62) [a]	< 0.001	1.42 (1.21–1.66) [b]	< 0.001
HFpEF	1.55 (1.37–1.76)	< 0.001	1.50 (1.31–1.71) [a]	< 0.001	1.41 (1.20–1.68) [b]	< 0.001
HFrEF	1.22 (0.98–1.53)	0.077	1.36 (1.02–1.81) [a]	0.038	1.60 (1.07–2.38) [b]	0.022

HFpEF heart Failure with Preserved Ejection Fraction, *HFrEF* heart Failure with Reduced Ejection Fraction, *eGFR* estimated glomerular filtration rate, *ACEI* angiotensin-converting enzyme inhibitor; *ARB* angiotensin receptor blocker; *LVEF* Left Ventricular Ejection Fraction; *BMI* body mass index. Odds ratios (95% confidence intervals) express the risk of the worsening renal function (WRF) associated with the doubling of the average furosemide equivalent dose.

[a]Adjusted models accounted for age, gender, SBP, diabetes, atrial fibrillation, Na, LVEF, eGFR, ACEI/ARB, spironolactone, statin and BB.

[b]Adjusted for age, gender, BMI, SBP, diabetes, atrial fibrillation, Na, LVEF, eGFR, ACEI/ARB, spironolactone, statin and BB. Patients with documented bmi: all patients $n = 874$, HFpEF patients $n = 573$ and HFrEF patients $n = 301$.

Sensitivity analysis

In the sensitivity analysis (Table 3), the crude odds ratios relating the risk of WRF to use of intravenous furosemide were 1.26 ($p < 0.001$) in all patients and 1.26 ($p = 0.002$) in patients with HFpEF. After adjusted for potential confounders, the odds ratios remained significant. By contrast, both crude and multivariable-adjusted odds ratios were not statistically significant in patients with HFrEF ($p \geq 0.099$).

Table 3
The Association of Risk Of WRF with Intravenous Furosemide.

HF categories	UNADJUSTED		ADJUSTED		FULLY ADJUSTED	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
ALL	1.39 (1.26–1.54)	< 0.001	1.42 (1.21–1.66) [a]	< 0.001	1.26 (1.09–1.44) [b]	< 0.001
HFpEF	1.55 (1.37–1.76)	< 0.001	1.41 (1.20–1.68) [a]	< 0.001	1.26 (1.08–1.46) [b]	0.002
HFrEF	1.22 (0.98–1.53)	0.077	1.60 (1.07–2.40) [a]	0.022	1.31 (0.95–1.82) [b]	0.099

HFpEF heart Failure with Preserved Ejection Fraction, *HFrEF* heart Failure with Reduced Ejection Fraction, *eGFR* estimated glomerular filtration rate, *ACEI* angiotensin-converting enzyme inhibitor; *ARB* angiotensin receptor blocker; *LVEF* Left Ventricular Ejection Fraction; *BMI* body mass index. Odds ratios (95% confidence intervals) express the risk of the worsening renal function (WRF) associated with the intravenous furosemide. [a]Adjusted models accounted for age, gender, SBP, diabetes, atrial fibrillation, Na, LVEF, eGFR, ACEI/ARB, spironolactone, statin and BB.

[b]Adjusted for age, gender, BMI, SBP, diabetes, atrial fibrillation, Na, LVEF, eGFR, ACEI/ARB, spironolactone, statin and BB. Patients with documented bmi: all patients *n* = 874, HFpEF patients *n* = 573 and HFrEF patients *n* = 301.

Discussion

To our knowledge, our study is the first survey assessing the association of the risk of WRF with the average daily loop diuretics dose in ADHF and HF subtypes. Our key findings can be summarized as follows: (i) patients with HFpEF compared with those with HFrEF had higher prevalence of WRF; (ii) for a doubling of the average furosemide equivalent dose, the multivariable-adjusted odds of WRF increased by 42% in all patients, by 41% in patients with HFpEF and by 60% in patients with HFrEF; and (iii) there was no interaction between heart failure categories and average furosemide equivalent dose.

Loop diuretics is the mainstay treatment for decongestion and has been widely used to relieve congestion in heart failure patients. However, higher dose of loop diuretic therapy is strictly associated with renal injury as well as mortality[3, 7]. Renal impairment characterized by WRF is a common comorbidity and confers high risk of poor prognosis in ADHF. In the COACH study, 11% of the patients developed WRF during hospitalization and WRF had a higher incidence of all-cause of mortality and heart failure admissions[17]. Among 233 patients (43.3% women; mean age, 72.2 years) with ADHF, 48 patients over 35.4 month (mean) had WRF at 1 year after discharge. The WRF at 1 year after discharge was a strong and independent predictor of all-cause and cardiovascular mortality[11]. Dose increases for loop diuretics between hospital discharge and 1 year afterwards were significantly larger in patients with 1-year WRF

than those in the non-WRF group[11]. In line with our findings, Butler and colleagues demonstrated that higher doses of loop diuretics in ADHF patients is associated with the occurrence of WRF[7].

Furthermore, the high risk of WRF in ADHF patients is associated with several pathophysiological processes, including hemodynamic status, activation of the neurohormonal system, the release of inflammatory cytokines and other drug therapies[18–20]. Plasma volume reduction leads to WRF in ADHF patients in whom high loop diuretic dose were administered[21]. Aggressive diuresis leading to plasma volume reduction is understandable since higher loop diuretic dose causes acute decrease in both pulmonary wedge pressure, cardiac output and triggers neurohormonal cascade[7, 22, 23]. These responses lead to vascular under-filling to the kidneys causing hypoperfusion. More sodium to the distal convoluted tubules to be reabsorbed that further reduced glomerular filtrate rate and thereby worsening renal function[21].

Recently, it has been put forward that HFpEF and HFrEF were distinct disease entities[24]. Takei and colleagues demonstrated that HFpEF and HFrEF patients have different sensitivity to plasma volume change after decongestion, which might lead to different responses reflecting in the renal function to diuretics dose increase[14]. This study proved the usage of high loop diuretics related to increased WRF in HFpEF patients. However, no previous study has elucidated the potential distinct effects of loop diuretic dosage on WRF in HFpEF and HFrEF patients. The higher incidence in WRF in HFpEF than HFrEF could be related to that HFpEF patients suffered from volume distribution rather than volume overload in HFrEF patients [14, 25]. HFpEF patients have impaired plasma filling rates, and frequent and high dose diuretic treatment leads to depletion of circulating volume[26–28]. The mechanism for the alternation of plasma volume is different amongst the HF categories, as Takei et al. reported plasma volume reduction after diuretic therapy was more common amongst HFpEF patients than HFrEF[14]. Together with the finding that HFpEF phenotype has a high dependence on preload, it is readily comprehensible that frequent aggressive diuresis can lead to decreased cardiac output and renal perfusion as a whole[29, 30].

Strengths And Limitations

Our current study should be interpreted within the context of its possible limitations and strengths. Among the potential limitations of our current study is its retrospective design, which generated a great deal of missed data, such as body mass index. Approximately 37.5% patients had missing body mass index. However, patients with body mass index were on average 5.8 years older ($p < 0.001$). Also, patients with and without body mass index had a similar systolic and diastolic blood pressure ($p \leq 0.091$), and included proportionally a similar number of women and smokers ($p \leq 0.069$). Second, we failed to examine the association of incident WRF with the average furosemide equivalent dose, thus long-term follow-up will be required. Third, our current findings in Chinese patients cannot be extrapolated to other ethnicities. On the contrary, to the best of our knowledge, our current study is the first to report on the association between the risk of WRF and the average furosemide equivalent dose among HF subtypes. Our study had a relatively large sample size and consistent observations irrespective of adjustment for potential confounders. HF is an increasingly significant global health challenge and imposes major

cardiovascular health burden due to high hospitalization, morbidity, and mortality rates. Although patients with HFpEF and HFrEF have different clinical characteristics and survival status, our study highlights the necessity to monitor the effect of loop diuretics on renal function in both HF subtypes.

Conclusion

In this study, patients with HFpEF and HFrEF had relatively high risk of WRF. The risk of WRF was associated with higher furosemide dosage in both HF subtypes. From a clinical point of view, our current study underlines the importance to screen for use of loop diuretics in both HFpEF and HFrEF to prevent the renal impairment.

Abbreviations

HFpEF
Heart failure patients with preserved ejection fraction
HFrEF
Heart failure patients with reduced ejection fraction
WRF
Worsening renal function
HF
Heart failure
ADHERE
Acute Decompensated Heart Failure National Registry
SBP
Systolic blood pressure
BMI
Body mass index
Na
Sodium
eGFR
Estimated glomerular filtration rate
LVEF
Left ventricular ejection fraction
BB
Beta-blockers
ACEI
Angiotensin-converting enzyme inhibitors
ARB
Angiotensin receptor blocker.

Declarations

Acknowledgement

Not applicable.

Contributors

Under the supervision of Chen Liu, Marvin Owusu-Agyeman, Xin He and Fang Fei performed in data preparation, study design, and statistical analysis. Marvin Owusu- Agyeman, Xin He, and Wei Hao Liang drafted the original article. Chen Liu and Fang Fei revised the draft. All authors read and ensured the accuracy of the data in the manuscript before submission.

Competing interest

All authors declare that they have no competing interest.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to lack of permit from the hospital to share the data, but are available from the corresponding author on reasonable request.

Ethics and approval to participate.

All study protocols involving human participants were in accordance with ethical standards of the Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

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Figures

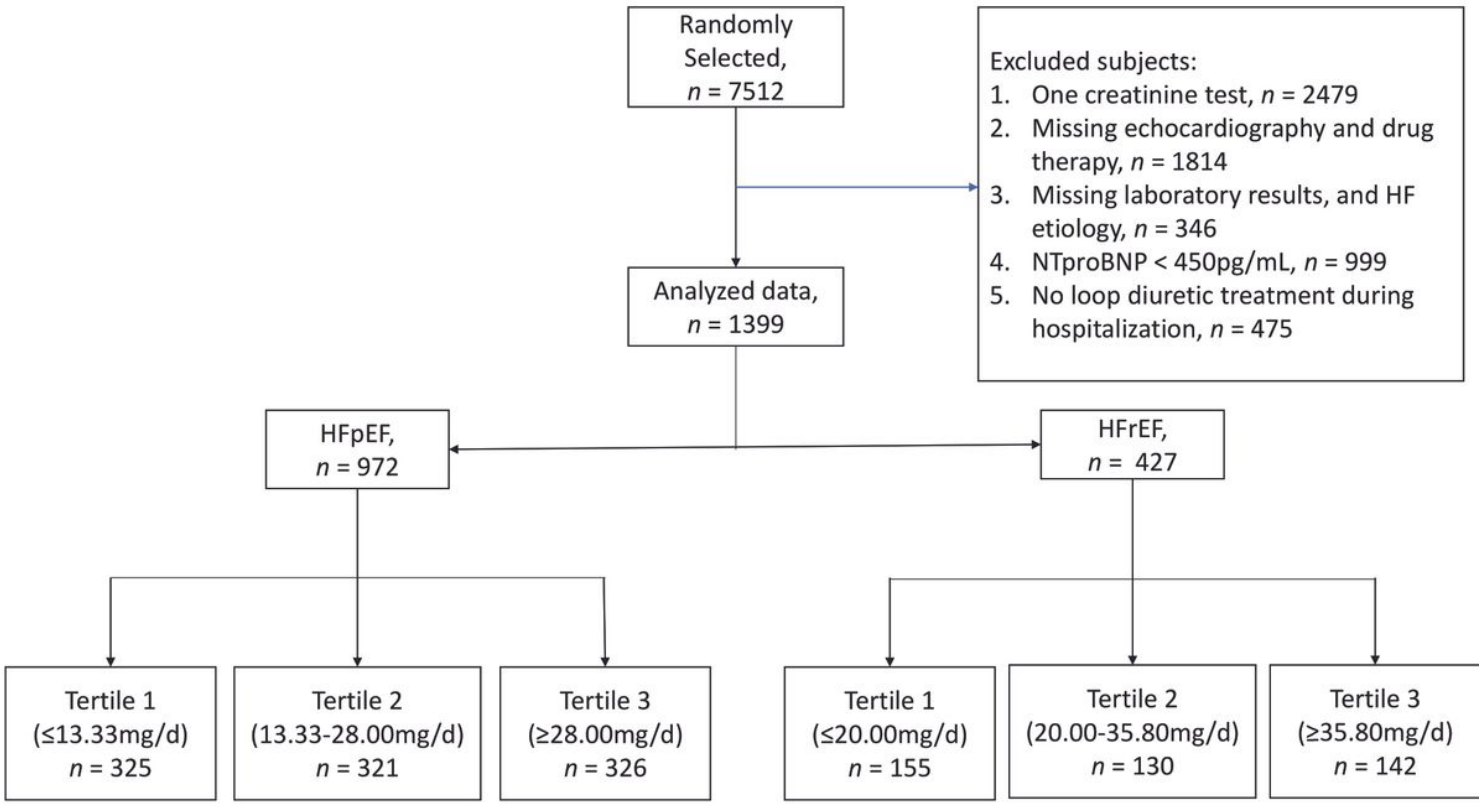

Figure 1

Patient flow chart in HFpEF (heart failure with preserved ejection fraction) and HFrEF (heart failure with reduced ejection fraction).

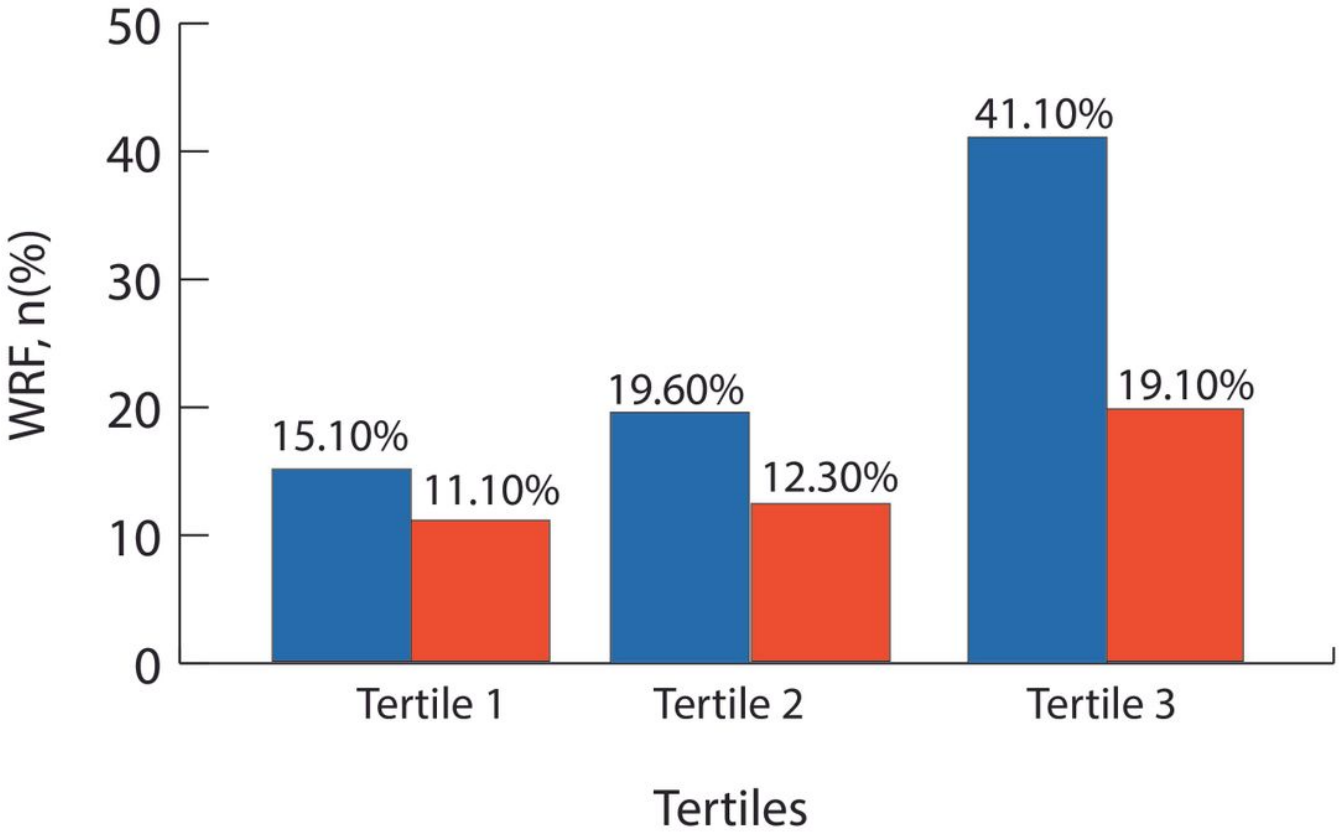

Figure 2

The prevalence of WRF between HFpEF and HFrEF patients by tertiles of average daily furosemide equivalent doses. HFpEF, heart failure with preserved ejection Fraction; HFrEF, heart failure with reduced ejection fraction.