ORIGINAL RESEARCH

Prognostic Value of Anxiety Between Heart Failure With Reduced Ejection Fraction and Heart Failure With Preserved Ejection Fraction

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***Background*—**Evidence suggests differences in clinical characteristics, causes, and prognoses between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Most studies have failed to support the prognostic relevance of anxiety in HFrEF or unclassified HF with mean left ventricular ejection fraction <40%. Meanwhile, the association between anxiety and prognoses in HFpEF remains unexamined. This study compared the prognostic value of anxiety between HFrEF and HFpEF.

***Methods and Results*—**A total of 158 patients with HFrEF (left ventricular ejection fraction=28.51±7.53%) and 108 patients with HFpEF (left ventricular ejection fraction=64.53±9.67%) were recruited between May 2012 and December 2014. Demographic and clinical characteristics, Spielberger State-Trait Anxiety Inventory, Beck Depression Inventory-II scale, and 18-month follow-up outcomes were recorded during the hospital stay. There were significant differences in age, sex, comorbidities, laboratory biomarkers, discharge medications, and unhealthy behaviors, which supported the contention that HFrEF and HFpEF represent 2 distinct phenotypes, although there were no significant differences in anxiety and 18-month outcomes. Multiple logistic regression yielded no significant associations between anxiety and 18-month outcomes in HFrEF. By contrast, trait anxiety could predict 18-month all-cause mortality (odds ratio, 1.429; 95% CI, 1.020–2.000; *P*=0.038), all-cause readmission or death (odds ratio, 1.147; 95% CI, 1.036–1.271; *P*=0.008), and cardiac readmission or death (odds ratio, 1.133; 95% CI, 1.031–1.245; *P*=0.010) in HFpEF after adjusting for possible confounders.

***Conclusions*—**Trait anxiety was independently associated with 18-month all-cause mortality, all-cause readmission or death, and cardiac readmission or death in HFpEF, but not in HFrEF. **(*J Am Heart Assoc*. 2019;8:e010739. DOI: 10.1161/JAHA.118.010739.)**

Key Words: heart failure with preserved ejection fraction • heart failure with reduced ejection fraction • mortality • readmission • trait anxiety

Both depression and anxiety are common in patients with heart failure (HF).[1–3] Considerable research supports the fact that depression is an independent predictive factor for mortality and readmission in patients with HF.[3,4] However, evidence of the impact of anxiety on mortality and readmission among patients with HF varies, and studies disagree whether there is a significant[5,6] or insignificant association that exists between the 2 prognoses.[6–14]

According to the 2016 European Society of Cardiology Heart Failure Guidelines, most cases of HF can be divided into HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] <40%) and HF with preserved ejection fraction (HFpEF; LVEF ≥50%).[15] Despite many similarities in symptoms and signs, the results of review studies indicate that HFrEF and HFpEF have different clinical characteristics (ie, bimodal EF distribution and response to therapies) and pathophysiological mechanisms (ie, ventricular remodeling, endothelial dysfunctions, and vascular stiffness).[16]

Evidence suggests that patients with HFpEF tend to be older, women, and more likely to have age-related comorbidities (eg, hypertension, diabetes mellitus, obesity, or kidney disease) than do those with HFrEF.[15,16] Furthermore, patients with HFpEF mainly tend to develop microvasculature dysfunction, particularly concentric remodeling induced by

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Clinical Perspective

What Is New?

- This study differentiated heart failure with preserved ejection fraction (HFpEF) from heart failure with reduced ejection fraction (HFrEF) phenotypes to compare the prognostic value of anxiety on 18-month outcomes, including all-cause mortality, cardiac mortality, all-cause readmission or death, and cardiac readmission or death.
- No significant differences were identified between HFrEF and HFpEF with respect to the prevalence of elevated trait anxiety and 18-month outcomes.
- This is the first study to examine the prognostic relevance of anxiety symptoms in a consecutive cohort of patients with HFpEF; trait anxiety in patients with HFpEF, but not in those with HFrEF, during their hospital stay independently predicted 18-month prognostic outcomes, including all-cause mortality, all-cause readmission or death, and cardiac readmission or death.

What Are the Clinical Implications?

- These findings supported the need to differentiate HFpEF from HFrEF phenotypes to evaluate the association between anxiety and prognostic outcomes.
- With respect to the prognostic relevance of psychological distresses in patients with HF, clinicians and researchers should emphasize HFpEF as well as HFrEF phenotypes.
- Cardiac rehabilitation programs and therapy, especially those targeting anxiety symptoms, should involve the HFpEF phenotype, which has been overlooked in previous studies.

hypertension, endothelial dysfunction, and vascular stiffness, and also age-related comorbidities; by contrast, HFrEF patients predominantly develop in response to myocardial insults, which are typically eccentric hypotrophy and large-scale myocyte loss.[16,17]

In terms of the prognostic value of anxiety, most of the results have failed to support the impact of anxiety in HFrEF or unclassified HF with mean LVEF <40%[6–14]; however, only one did find support for the impact from anxiety in unclassified HF with mean LVEF >40%.[5] Meanwhile, the association between anxiety and HFpEF remains unexplored. Nevertheless, anxiety activates sympathetic nerve function[18–20] and the renin-angiotensin system,[21] both of which are the physiopathological mechanisms of all HF phenotypes. Empirical studies have found support for the premise that anxiety is associated with HFpEF-related mechanisms, particularly adrenomedullin,[22] endothelial dysfunction,[23–25] vascular stiffness,[26–28] and age-acquired comorbidities, including accelerated aging,[29,30] diabetes mellitus,[31] obesity,[32] and hypertension.[33] Few studies have supported the association between anxiety and myocardial insults, which are the predominant mechanisms of HFrEF. Consequently, we have inferred that the psychopathological correlates of anxiety are more often associated with HFpEF than with HFrEF.

The purpose of this study was, therefore, to compare the prognostic value of anxiety in patients with HFrEF and HFpEF. On the basis of the psychopathological correlates, we hypothesized that anxiety is more influential in the prognosis of HFpEF than in the prognosis of HFrEF.

Methods

Study Participants and Procedures

Between May 2012 and December 2014, a prospective cohort was used to recruit 328 consecutive inpatients with clinically diagnosed HF undergoing treatment at 2 regional teaching hospitals in Taiwan (Buddhist Dalin Tzu Chi Hospital and Buddhist Taipei Tzu Chi Hospital). Prospective participants were approached for this study during their hospital stay. Inclusion criteria included complete New York Heart Association functional class and LVEF. After excluding 41 patients with HF with midrange ejection fraction (LVEF 40%–49%), 5 patients with psychiatric disorders, and 16 patients with incomplete questionnaires, the final analyses were conducted on data for 266 patients (158 with HFrEF and 108 with HFpEF).

The study protocol was approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Research Ethics Committee (No. B10004009-1), and written informed consent was obtained from each patient. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Researchers interested in the data, methods, or analysis can contact the corresponding author for more information.

Baseline Characteristics

While in the hospital, all participants filled out a detailed questionnaire that was used to assess demographic and clinical characteristics, including age, sex, educational level, marital status, surgical history, and family history of cardiovascular disease. Certain unhealthy behaviors were assessed by means of the self-reported questionnaire, including smoking (cigarettes per day), drinking alcohol (drinks per day), and lack of exercise (incompatible with 30 minutes of exercise 3 days per week or most days). Other data, such as laboratory tests (body mass index, heart rate, QRS duration, systolic pressure, diastolic pressure, and hemoglobin levels), comorbidities (presence of stroke, respiratory disease, kidney disease, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation, and coronary artery disease), and discharge medications (diuretics, angiotensin-converting

enzyme inhibitors, β blockers, angiotensin II receptor blockers, calcium channel blockers, and digoxin), were retrospectively collected from electronic medical records during the patients' hospital stay.

Anxiety and Depression Assessments

The Spielberger State-Trait Anxiety Inventory (STAI) is commonly used to measure anxiety symptoms, including state anxiety and trait anxiety.[34] The Chinese version of the STAI, translated and revised by Chung and Long,[35] exhibits favorable internal consistency reliability (Cronbach's α=0.93) and was used for this study. Test-retest reliability was found to be 0.737 for the State-Anxiety Subscale and 0.755 for the Trait-Anxiety Subscale for a 1-week interval.[35] In addition, test-retest reliability for the original Trait-Anxiety Subscale has ranged from 0.73 to 0.86. For the original State-Anxiety Subscale, the test-retest reliability has been relatively low, ranging from 0.16 to 0.62. State anxiety refers to a transitory change that a person experiences as an emotional state at the moment or when he or she perceives some type of threat under specific conditions. This may fluctuate over time and can vary in intensity. Trait anxiety, a stable and persistent style of anxiety, is defined as the relative vulnerability of an individual and a general proneness to experience anxiety in response to and in anticipation of threats in the environment.[36] People with higher degrees of trait anxiety experience more threats or dangers across time and situations with more intense anxiety than do those with lower trait anxiety stably.[36] The STAI Trait-Anxiety Subscale measures relatively stable aspects of "anxiety proneness," including lack of the general states of calmness, confidence, and security.[34] By contrast, the STAI State-Anxiety Subscale measures how anxious participants feel "right now," including feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system.[34] Each Chinese version of the STAI Subscale comprises 20 items scored on 4-point Likert-type scales, from 1 (*not at all*) to 4 (*very much so*).[34] Total scores for each subscale range from 20 to 80, with higher total scores indicating more and worse anxiety symptoms.[34] A cutoff score of ≥40 for elevated state anxiety and trait anxiety has been used for patients with cardiovascular disease.[11,37] Depressive symptoms were measured with the Chinese version of the Beck Depression Inventory-II (BDI-II).[38] The Chinese version of the BDI-II has good internal consistency reliability (Cronbach's α=0.94) and is a self-reported, 21-item questionnaire that assesses the current severity of depression symptoms in various populations. Each Chinese version BDI-II item is scored on a scale of 0 (absent) to 3 (severe), with higher total scores indicating more severe depressive symptoms. Furthermore, the BDI-II has been widely used for assessing the intensity of depression in cardiac populations.[39] In this study, all participants completed the Chinese versions of the BDI-II and STAI at baseline.

Follow-Up Outcomes

Follow-up outcomes were ascertained 18 months after discharge, using the electronic medical records database or through direct contact by telephone. According to the *International Classification of Diseases, Ninth Revision* (*ICD-9*), the 4 main outcomes included the following: (1) all-cause mortality, (2) cardiac mortality, (3) all-cause readmission or death, and (4) cardiac readmission or death. All-cause end points were defined as all causes of end points occurring in a population, including cardiac-related causes and noncardiac causes. Cardiac-related end points were based on the records of cardiovascular events or obtained from the cardiac wards (either internal medicine or surgical ward). Follow-up data 18 months after discharge were obtained from all participants.

Statistical Analysis

According to the 2016 European Society of Cardiology Heart Failure Guidelines, patients were divided into 2 groups, HFrEF (LVEF <40%) and HFpEF (LVEF ≥50%). Categorical variables are expressed as a number with percentage, and continuous variables are expressed as median±interquartile range. This study used Fisher's exact test for categorical variables and the median test for continuous variables without the normal distribution (P<0.05 in the Kolmogorov-Smirnov test), to determine group differences in baseline characteristics, STAI subscales, BDI-II scores, and outcomes. The correlation between State-Anxiety Subscale and Trait-Anxiety Subscale scores and their correlation with BDI-II scores between groups were examined with the Pearson correlation coefficient. Univariate and multiple logistic regression analyses were conducted to determine the impacts of the State-Anxiety and Trait-Anxiety Subscale scores on each 18-month end point for both groups, including the following: (1) all-cause mortality in all participants, (2) cardiac mortality after excluding participants with noncardiac mortality caused by mutually exclusive events for cardiac and noncardiac mortalities, (3) all-cause readmission or death, and (4) cardiac readmission or death. In multiple logistic regression, this study adjusted for sex, age, education level, marital status, LVEF, New York Heart Association functional class, BDI-II score, surgical history, smoking, drinking, lack of exercise, family history of cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation, and coronary artery disease, and the use of diuretics, angiotensin-converting enzyme inhibitors, β blockers, angiotensin II receptor blockers, calcium channel blockers, and digoxin.

To build the model, we simultaneously added possible covariates to the multiple logistic regression. Demographic variables (age, sex, education level, marital status, surgical history, and family history of cardiovascular disease) and discharge medications (use of diuretics, angiotensin-converting enzyme inhibitors, β blockers, angiotensin II receptor blockers, calcium channel blockers, and digoxin) were entered as standard covariates in this model as they were commonly included in prior research for assessing relevant prognostic risks for patients with HF[4–14] or in the 2016 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF.[15] To select covariates in this analysis, New York Heart Association functional class, LVEF, and comorbidities (stroke, respiratory disease, kidney disease, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and coronary artery disease) were considered markers of worse prognosis in patients with HF.[15] In addition, this study compared the prognostic value of anxiety in patients with HFrEF and HFpEF and included the potential influence of behavioral pathways, such as smoking, drinking, and lack of exercise, as covariates for establishing the direct psychopathological correlates of anxiety.

Odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) for each of the anxiety measures were reported for multiple logistic regressions. The exponential function of the regression coefficient is the ORs of the prognostic outcomes related with a 1-unit increase in continuous variables about anxiety and depression symptoms. The Hosmer and Lemeshow test was used to determine goodness of fit in the multiple logistic regression models, and a nonsignificant *P* value indicated a good fit. All analyses were performed with SPSS, version 22.0 (SPSS Inc, Chicago, IL), and a 2-tailed test result of $P<0.05$ indicated statistical significance.

Results

Baseline Characteristics of Patients With HFrEF and HFpEF

During the study period, a total of 266 patients with clinically diagnosed HF met the inclusion criteria and completed follow-up procedures, including 158 patients with HFrEF (LVEF=28.51±7.53%) and 108 patients with HFpEF (LVEF=64.53±9.67%). All baseline characteristics during the hospital stay in patients with HFrEF versus HFpEF were shown in Table 1. For the demographic characteristics, patients with HFpEF were older (64.50 versus 59.00 years; $P=0.013$), more often women than men (49.1% versus 22.8%; $P<0.001$), and more likely to have a history of surgery (61.1% versus 43.0%; $P=0.004$) than patients with HFrEF. However, the indicator of symptom severity, New York Heart Association functional class, did not differ between

Table 1. Baseline Characteristics of the Patients With HFrEF Versus Those With HFpEF

Variable	Patients With HFrEF (n=158)	Patients With HFpEF (n=108)	*P* Value*
Age, median±IQR, y	59.00±17.00	64.50±16.00	0.013
Female sex, n (%)	36 (22.8)	53 (49.1)	<0.001
Education level, n (%)			
Low	69 (43.7)	56 (51.9)	0.443
Medium	68 (43.0)	40 (37.0)	
High	21 (13.3)	12 (11.1)	
Having a spouse, n (%)	99 (62.7)	77 (71.3)	0.150
CVD family history, n (%)	70 (44.3)	36 (33.3)	0.076
Surgical history, n (%)	68 (43.0)	66 (61.1)	0.004
NYHA functional class, n (%)			
I	2 (1.3)	4 (3.7)	0.208
II	41 (25.9)	37 (34.3)	
III	57 (36.1)	30 (27.8)	
IV	58 (36.7)	37 (34.3)	
Comorbidity, n (%)			
Diabetes mellitus	62 (39.2)	48 (44.4)	0.447
Hypertension	84 (53.2)	74 (68.5)	0.016
Hypercholesterolemia	26 (16.5)	20 (18.5)	0.742
Coronary artery disease	86 (54.4)	55 (50.9)	0.618
Atrial fibrillation	50 (31.6)	43 (39.8)	0.191
Stroke	15 (9.5)	5 (4.6)	0.162
Kidney disease	34 (21.5)	35 (32.4)	0.047
Respiratory tract disease	8 (5.1)	15 (13.9)	0.015
Tumors	5 (3.2)	8 (7.4)	0.149
Discharge medication, n (%)			
Diuretics	125 (79.1)	65 (60.2)	0.001
β Blockers	79 (50.0)	45 (41.7)	0.211
Angiotensin-converting enzyme inhibitors	41 (25.9)	16 (14.8)	0.033
Angiotensin II receptor blockers	74 (46.8)	34 (31.5)	0.016
Calcium channel blockers	25 (15.8)	32 (29.6)	0.009
Digoxin	36 (22.8)	10 (9.3)	0.005
Laboratory test, median±IQR			
BMI, kg/m^2	25.24±5.97	25.98±8.34	0.526
Heart rate, bpm	92±24	77±23.5	<0.001
QRS duration, ms	100±30	94±20	0.022
SBP, mm Hg	129±37	140±46	0.001
DBP, mm Hg	84±21.5	78±26	0.039

Continued

Table 1. Continued

Variable	Patients With HFrEF (n=158)	Patients With HFpEF (n=108)	*P* Value*
PP, mm Hg	46±20.5	62±36	<0.001
Hemoglobin, g/dL	13.5±3.6	12±4.5	0.005
Unhealthy behavior, n (%)			
Smoking	84 (53.2)	34 (31.5)	0.001
Drinking alcohol	38 (24.1)	10 (9.3)	0.003
Lack of exercise	47 (29.7)	35 (32.4)	0.686

BMI indicates body mass index; bpm, beats per minute; CVD, cardiovascular disease; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; NYHA, New York Heart Association; PP, pulse pressure; SBP, systolic blood pressure.
*Fisher's exact test was used for categorical variables, and the median test was used for continuous variables because of nonnormal distribution.

the 2 groups. The analysis of comorbidities indicated that patients with HFpEF had higher rates of hypertension (68.5% versus 53.2%; *P*=0.016), kidney disease (32.4% versus 21.5%; *P*=0.047), and respiratory tract disease (13.9% versus 5.1%; *P*=0.015). For the use rates of discharge medications, diuretics (79.1% versus 60.2%; *P*=0.001), angiotensin-converting enzyme inhibitors (25.9% versus 14.8%; *P*=0.033), angiotensin II receptor blockers (46.8% versus 31.5%; *P*=0.016), and digoxin (22.8% versus 9.3%; *P*=0.005) were more frequently used by patients with HFrEF; by contrast, a calcium channel blocker (15.8% versus 29.6%; *P*=0.009) was more frequently used by patients with HFpEF. For laboratory data, there were significant differences between patients with HFrEF and HFpEF in heart rate (92 versus 77 beats per minute; *P*<0.001), QRS duration (100 versus 94 ms; *P*=0.022), systolic blood pressure (129 versus 140 mm Hg; *P*=0.001), diastolic blood pressure (84 versus 78 mm Hg; *P*=0.039), pulse pressure (46 versus 62 mm Hg; *P*<0.001), and hemoglobin (13.5 versus 12 g/dL; *P*=0.005). Finally, patients with HFpEF exhibited fewer unhealthy behaviors than patients with HFrEF, including smoking (31.5% versus 53.2%; *P*=0.001) and drinking alcohol (9.3% versus 24.1%; *P*=0.003).

Psychological Factors at Baseline

The median STAI State-Anxiety and Trait-Anxiety Subscale scores were shown in patients with HFrEF (35±11 and 33±13 scores, respectively) and HFpEF (35±11 and 32.5±11 scores, respectively). Elevated rates of state anxiety and trait anxiety (scores ≥40) were also reported in patients with HFrEF (31.6% and 27.2%, respectively) and HFpEF (28.7% and 24.1%, respectively). However, no differences were identified between the 2 groups in median State-Anxiety Subscale scores (*P*=0.447), median Trait-Anxiety Subscale scores (*P*=0.606), elevated rate of state anxiety (*P*=0.684), and trait anxiety (*P*=0.573). The median BDI-II scores in patients with HFrEF and HFpEF were 4±4.5 and 3±4 scores, respectively. The prevalence of elevated depression scores (≥14) was 10.1% in patients with HFrEF and 3.7% in patients with HFpEF. Patients with HFrEF had higher median BDI-II scores (*P*=0.031) and elevated rate of depressive symptoms (*P*=0.050) than did patients with HFpEF (Table 2). In addition, STAI State-Anxiety Subscale scores were highly associated with Trait-Anxiety Subscale scores in the 2 groups (HFrEF, *r*=0.722 [*P*<0.001]; HFpEF, *r*=0.711 [*P*<0.001]). The BDI-II score was highly correlated with State-Anxiety and Trait-Anxiety scores in patients with HFrEF (*r*=0.504 and 0.643, respectively; *P*<0.001) and HFpEF (*r*=0.501 and 0.637, respectively; *P*<0.001).

Outcomes at 18-Month Follow-Up

In terms of mortality, 27 of 158 patients (17.1%) with HFrEF and 15 of 108 patients (13.9%) with HFpEF died from any cause. A total of 18, 14 of 145 (9.7%) and 4 of 97 (4.1%), were attributable to a cardiac cause in patients with HFrEF and HFpEF, respectively. In terms of readmission, there was a 53.8% (85/158) prevalence of all-cause readmission or death in patients with HFrEF and a 52.8% (57/108) prevalence of all-cause readmission or death in patients with HFpEF. In addition, 68 of 158 patients with HFrEF (43.0%) and 35 of 108 patients with HFrEF (32.4%) had cardiac readmission or death. However, no differences were found between patients with HFrEF and HFpEF in all four 18-month outcomes (all *P*>0.05; Table 3).

Table 2. Psychological Factors and Elevated Psychological Distresses of Patients With HFrEF Versus Those With HFpEF at Baseline

Variables	Patients With HFrEF	Patients With HFpEF	*P* Value*
Psychological factor, median±IQR			
State-Anxiety Subscale scores	35±11	35±11	0.447
Trait-Anxiety Subscale scores	33±13	32.5±11	0.606
BDI-II scores	4±4.5	3±4	0.031
Elevated psychological distress, n (%)			
State-Anxiety Subscale scores ≥40	50 (31.6)	31 (28.7)	0.684
Trait-Anxiety Subscale scores ≥40	43 (27.2)	26 (24.1)	0.573
BDI-II scores ≥14	16 (10.1)	4 (3.7)	0.050

BDI-II indicates Beck Depression Inventory-II; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range.
*Fisher's exact test was used for categorical variables, and the median test was used for continuous variables because of nonnormal distribution.

Table 3. Outcomes at 18 Months of Patients With HFrEF Versus Those With HFpEF

Outcomes	Patients With HFrEF	Patients With HFpEF	*P* Value
All-cause mortality			
No. (%)	27 (17.1)	15 (13.9)	0.608
Total no.	158	108	
Cardiac mortality			
No. (%)	14 (9.7)	4 (4.1)	0.136
Total no.	145	97	
All-cause readmission or death			
No. (%)	85 (53.8)	57 (52.8)	0.901
Total no.	158	108	
Cardiac readmission or death			
No. (%)	68 (43.0)	35 (32.4)	0.096
Total no.	158	108	

HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Prognostic Value of State-Anxiety, Trait-Anxiety, and Depression

On the basis of the differentiation between HFrEF and HFpEF phenotypes, neither State-Anxiety nor Trait-Anxiety Subscale scores were significantly associated with any unadjusted 18-month outcomes in patients with HFrEF (all $P>0.05$; Table 4). However, except for cardiac readmission or death, both State-Anxiety and Trait-Anxiety Subscale scores were significantly associated with unadjusted all-cause mortality (OR, 1.073; 95% CI, 1.013–1.137; $P=0.016$; and OR, 1.081; 95% CI, 1.007–1.161; $P=0.032$; respectively) and all-cause readmission or death (OR, 1.060; 95% CI, 1.014–1.109; $P=0.011$; and OR, 1.068; 95% CI, 1.011–1.128; $P=0.019$; respectively) in patients with HFpEF (Table 4). Depression scores (BDI-II) failed to predict any unadjusted 18-month outcomes in patients with both HFrEF and HFpEF (all $P>0.05$; Table 4). To evaluate cardiac mortality as an outcome, one must account for noncardiac mortality in a competing risk model. However, competing risk models require event dates, which were not available in our data set. We also performed interaction tests on anxiety and group by pooling HFrEF and HFpEF samples in the unadjusted logistic regression. We found the interaction effect of Trait-Anxiety Subscale score and group (Trait-Anxiety×group) was significant in all-cause mortality ($\beta=0.087$; $P=0.046$) but not significant in all-cause readmission or death ($\beta=0.052$; $P=0.115$) and cardiac readmission or death ($\beta=0.032$; $P=0.339$). In addition, the interaction effect of State-Anxiety Subscale score and group (State-Anxiety×group) was not significant in all 4 prognostic outcomes ($P>0.05$).

Table 4. Univariate Logistic Regression of State-Anxiety, Trait-Anxiety, and Depression for 18-Month Outcomes in Patients With HFrEF Versus Those With HFpEF

	Patients With HFrEF			Patients With HFpEF		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value
All-cause mortality						
State-Anxiety	1.020	0.974–1.068	0.396	1.073	1.013–1.137	0.016
Trait-Anxiety	0.991	0.945–1.039	0.711	1.081	1.007–1.161	0.032
Depression	1.014	0.957–1.075	0.640	1.025	0.923–1.138	0.649
All-cause readmission or death						
State-Anxiety	1.022	0.989–1.059	0.235	1.060	1.014–1.109	0.011
Trait-Anxiety	1.013	0.978–1.050	0.464	1.068	1.011–1.128	0.019
Depression	1.023	0.974–1.075	0.358	1.015	0.936–1.101	0.715
Cardiac readmission or death						
State-Anxiety	1.017	0.981–1.053	0.366	1.030	0.987–1.076	0.174
Trait-Anxiety	1.021	0.985–1.058	0.252	1.054	0.998–1.113	0.059
Depression	1.021	0.974–1.070	0.394	0.974	0.889–1.069	0.583

The interaction effect of the Trait-Anxiety×group was significant in all-cause mortality ($P=0.046$), as well as nonsignificant in all-cause readmission or death ($P=0.115$) and cardiac readmission or death ($P=0.339$). The interaction effect of the State-Anxiety×group was not significant in all-cause mortality ($P=0.175$), all-cause readmission or death ($P=0.210$), and cardiac readmission or death ($P=0.634$). We were unable to conduct the univariate/multiple logistic regression analysis of cardiac mortality because relative competing risks were not considered. Data are given for each 1-unit increase in continuous variables for State-Anxiety, Trait-Anxiety, and Depression. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OR, odds ratio.

In the multiple logistic regression analyses adjusted for all potential confounders between HFrEF and HFpEF, there were no significant associations between anxiety or depression and 18-month outcomes in patients with HFrEF (all $P>0.05$; Table 5). However, Trait-Anxiety Subscale scores, but not State-Anxiety Subscale scores, were independently associated with all-cause mortality (OR, 1.429; 95% CI, 1.020–2.000; $P=0.038$), all-cause readmission or death (OR, 1.147; 95% CI, 1.036–1.271; $P=0.008$), and cardiac readmission or death (OR, 1.133; 95% CI, 1.031–1.245; $P=0.010$) in patients with HFpEF (Table 5). We also found State-Anxiety Subscale scores could predict all-cause readmission or death (OR, 1.075; 95% CI, 1.005–1.150; $P=0.036$). Depression scores (BDI-II) failed to predict any 18-month outcomes in patients

Table 5. Multiple Logistic Regression of State-Anxiety, Trait-Anxiety, and Depression for 18-Month Outcomes in Patients With HFrEF Versus Those With HFpEF

	Patients With HFrEF			Patients With HFpEF		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value
All-cause mortality						
State-Anxiety model						
State-Anxiety	1.043	0.969–1.123	0.264	1.502	0.966–2.337	0.071
Depression	0.965	0.865–1.077	0.528	0.604	0.252–1.450	0.259
H & L test	χ^2=9.858; P=0.275			χ^2=0.999; P=0.999		
Trait-Anxiety model						
Trait-Anxiety	1.007	0.932–1.089	0.853	1.429	1.020–2.000	0.038
Depression	0.995	0.892–1.109	0.926	0.629	0.345–1.147	0.130
H & L test	χ^2=12.505; P=0.130			χ^2=3.477; P=0.903		
All-cause readmission or death						
State-Anxiety model						
State-Anxiety	1.029	0.976–1.085	0.289	1.075	1.005–1.150	0.036
Depression	0.999	0.930–1.074	0.984	0.956	0.847–1.079	0.470
H & L test	χ^2=85.130; P=0.744			χ^2=7.971; P=0.436		
Trait-Anxiety model						
Trait-Anxiety	1.019	0.962–1.080	0.518	1.147	1.036–1.271	0.008
Depression	1.001	0.926–1.083	0.972	0.893	0.775–1.029	0.118
H & L test	χ^2=6.731; P=0.566			χ^2=8.350; P=0.400		
Cardiac readmission or death						
State-Anxiety model						
State-Anxiety	1.024	0.970–1.081	0.390	1.062	0.994–1.135	0.073
Depression	1.009	0.938–1.086	0.805	0.937	0.820–1.070	0.337
H & L test	χ^2=5.263; P=0.729			χ^2=8.890; P=0.352		
Trait-Anxiety model						
Trait-Anxiety	1.029	0.969–1.093	0.357	1.133	1.031–1.245	0.010
Depression	1.002	0.925–1.086	0.961	0.865	0.733–1.020	0.084
H & L test	χ^2=8.561; P=0.381			χ^2=9.122; P=0.332		

Adjusted for sex, age, education level, marital status, left ventricular ejection fraction, New York Heart Association functional class, Beck Depression Inventory-II score, surgical history, smoking, drinking alcohol, lack of exercise, family history of cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation, and coronary artery disease, and use of diuretics, angiotensin-converting enzyme inhibitors, β blockers, angiotensin II receptor blockers, calcium channel blockers, and digoxin. The interaction effect of the Trait-Anxiety×group was significant in all-cause mortality ($P=0.048$) and all-cause readmission or death ($P=0.048$), as well as borderline significant in cardiac readmission or death ($P=0.092$). The interaction effect of the State-Anxiety×group was not significant in all-cause mortality ($P=0.110$), all-cause readmission or death ($P=0.318$), and cardiac readmission or death ($P=0.397$). We were unable to conduct the multiple logistic regression analysis of cardiac mortality because the relative competing risks were not considered. Data are given for each 1-unit increase in continuous variables about State-Anxiety, Trait-Anxiety, and Depression. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; H & L, Hosmer and Lemeshow; OR, odds ratio.

with HFpEF (all $P>0.05$). The Hosmer and Lemeshow tests of goodness of fit in the multiple logistic regression analyses were satisfactory (all $P>0.05$). To evaluate cardiac mortality as an outcome, one must account for noncardiac mortality in a competing risk model. However, competing risk models require event dates, which were not available in our data set. We also performed interaction tests on anxiety and group by pooling HFrEF and HFpEF samples in the adjusted multiple logistic regression. We found the interaction effect of the Trait-Anxiety×group was significant in all-cause mortality ($\beta=0.349$; $P=0.048$) and all-cause readmission or death ($\beta=0.118$; $P=0.048$), as well as borderline significant in cardiac readmission or death ($\beta=0.096$; $P=0.092$). In addition, the interaction effect of the State-Anxiety×group was not significant in all 4 prognostic outcomes ($P>0.05$).

Discussion

To our knowledge, this is the first study to compare the prognostic value of anxiety on outcomes between inpatients with HFrEF and HFpEF. We confirmed the differences between inpatients with HFrEF and HFpEF phenotypes in demographic variables (age and sex), clinical characteristics (comorbidities, discharge medications, and laboratory biomarkers), psychological distress (anxiety and depression), unhealthy behaviors (smoking, drinking alcohol, and lack of exercise), and adverse outcomes. In addition, we examined the impact of anxiety on prognoses in patients with HFrEF and HFpEF phenotypes. An important finding of this study is that anxiety was associated with unadjusted or adjusted adverse outcomes in inpatients with HFpEF, but not in those with HFrEF. After the adjustment for all possible confounders, trait anxiety could still independently predict all-cause mortality, all-cause readmission or death, and cardiac readmission or death during 18-month follow-up in inpatients with HFpEF, but not in those with HFrEF.

The results of this study demonstrated that inpatients with HFpEF tend to be older and more often women, with higher levels of hypertension, kidney disease, and respiratory tract disease, and exhibit more use of calcium channel blockers and less use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and digoxin than inpatients with HFrEF, providing the evidence that age-acquired characteristics are more common in HFpEF.[16] Laboratory biomarkers show that inpatients with HFpEF have shorter QRS duration, higher systolic blood pressure, lower diastolic blood pressure, higher pulse pressure, and lower hemoglobin than inpatients with HFrEF, which indicated that HFpEF is prominently associated with loading abnormality and vascular stiffening. These results are consistent with those of previous studies.[16,40] Furthermore, this study found typical coronary risk factors for HFrEF, including male sex, high hemoglobin levels, smoking, and drinking alcohol, which are identically associated with HFrEF in response to myocardial insults.[41] Consistent with previous studies,[15,16,42] the different demographic and clinical characteristics found in this study supported the contention that HFrEF and HFpEF represent 2 distinct phenotypes.

This study identified no significant differences in the median score and elevated rate of State-Anxiety and Trait-Anxiety Subscale scores between inpatients with HFrEF and those with HFpEF. In addition, no significant differences were discerned in the 18-month follow-up outcomes, including all-cause mortality, cardiac mortality, all-cause readmission or death, and cardiac readmission or death between inpatients with HFrEF and those with HFpEF. Patients may feel threatened by the symptoms of the disease and the treatment process and, thus, their anxiety and depression levels may increase when they are inpatients. Therefore, we do not consider state anxiety and depression assessment to reflect long-term personalities or to be relevant to outcomes at the 18-month follow-up. By contrast, trait anxiety, which measures a patient's typical "in general" feelings of stress, worry, and discomfort on a day-to-day basis, reflects long-term personality, which should not be affected by the state of the illness at the time. Therefore, trait anxiety may be relevant to the outcomes at the 18-month follow-up.

By differentiating between HFrEF (LVEF <40%) and HFpEF (LVEF ≥50%) phenotypes, this is the first study to support the premise that anxiety, especially trait anxiety, independently predicts prognoses (all-cause mortality, all-cause readmission or death, and cardiac readmission or death) in inpatients with HFpEF, but not in those with HFrEF. Results of other studies in which anxiety was determined not to be significantly associated with prognostic outcomes may have been affected by the lack of clear distinctions between HFrEF and HFpEF phenotypes. For patients with unclassified HF with mean LVEF <40%, most of the results, except for 2 studies that used the categorical variable of anxiety,[6,9] reported that anxiety was not significantly associated with all-cause mortality and cardiac readmission (especially HF-related readmission) in inpatients[11,14] or outpatients[6–8,10,12,13] after adjusting for demographic and clinical variables. These results were in accordance with our findings in patients with HFrEF. In contrast to the results of patients with unclassified HF with mean LVEF <40%, only a single study supported an association between anxiety and HF-related readmission, a finding that was made using an unclassified HF sample with a mean LVEF of 48%.[5] This is consistent with our findings on patients with HFpEF (LVEF ≥50%). According to the aforementioned study, these results validated the contention that the associations between anxiety and prognostic outcomes in HF should be considered from the critical perspective of distinct HF phenotypes, particularly HFrEF and HFpEF.

We discerned no significant associations between depression and any prognostic outcomes in inpatients with either HFrEF or HFpEF. The mean value of the depression score was also relatively lower than that reported in previous studies.[3] One possible explanation for these results might be related to the Taiwanese National Health Insurance system, which provides good accessibility, comprehensive coverage, low cost, and high coverage rates. These strengths of the National Health Insurance system have decreased the occurrence and severity of depression symptoms and, thus, associated the cardiovascular risk factors since the implementation of the National Health Insurance system in Taiwan.[43] The other possible explanation for these results might be strong social support in Taiwan. Social support, including tangible support, perceived emotional support, and support satisfaction, is generally a robust predictor of change in depression among Taiwanese populations.[44]

Evidence has demonstrated that HFrEF and HFpEF phenotypes are based on fundamental differences in the extent of myocardial dysfunction, the pattern of remodeling, and the response to therapeutic treatment.[16] HFpEF tends to develop microvasculature dysfunctions, particularly hypertension with concentric remodeling, endothelial dysfunction, and ventricular-vascular stiffness. By contrast, HFrEF may develop in response to large-scale myocyte loss and eccentric hypotrophy.[16,17] As for the possible direct psychopathological correlates, these results suggest that anxiety was more influential in the prognoses of patients with HFpEF than in those with HFrEF. An abundance of empirical studies has supported the view that anxiety is strongly related to excessive microvasculature dysfunctions, including endothelial dysfunction[23–25] and vascular stiffness.[26–28] These microvascular dysfunctions have been independently associated with diastolic dysfunction and adverse outcomes in patients with HFpEF but not in patients with HFrEF.[45,46] Furthermore, compared with patients with hypertension but without anxiety, patients with hypertension and anxiety have been reported to have higher left ventricular mass indexes and adrenomedullin,[22] which tends to develop ventricular remodeling in HFpEF. Large cohort studies have demonstrated the adverse prognostic relevance of ventricular remodeling in patients with HFpEF[47,48] but not in patients with HFrEF. Such mechanisms provide a potential explanation for the prognostic findings in this study.

Some limitations of this study should be acknowledged. First, the sample sizes of both HF phenotypes were small; nevertheless, the sample was large enough to establish a relationship between anxiety and prognoses. Future studies should enroll more participants to improve research generalizability. Critically, further study with a larger sample size is required to examine the interaction effect of HF group and trait anxiety to determine whether trait anxiety predicts significantly different outcomes between the 2 HF phenotypes. Second, this study did not identify the exact number of days from the initial point to death or hospitalization. Future studies should use the Cox regression model, which is based on exact intervals of time and describes the probability of failure associated with precise time increments. Third, we cannot conduct the logistic regression analyses for cardiac mortality because the relative competing risks were not available in our data set, which did not include noncardiac deaths and event dates. Further study must take the relative competing risks and event dates into account. Finally, although we adjusted some of the behavioral pathways (smoking, drinking alcohol, and lack of exercise) in this study, other pathways (taking medications, diets, weight monitoring, and symptom management) should also be thoroughly studied.

Conclusions

This is the first study to differentiate inpatients with HFpEF from those with HFrEF and find the significant association between anxiety and prognostic outcomes (ie, all-cause mortality, all-cause readmission or death, and cardiac readmission or death) in inpatients with HFpEF, but not in those with HFrEF, although there were no significant differences of the median score and elevated rate of anxiety or the 18-month outcomes between these 2 phenotypes. With respect to prognostic outcomes of patients with HF, most previous studies have focused on either HFrEF or unclassified patients with HF and have overlooked patients with HFpEF. Thus, most of the study from earlier results failed to support the impact of anxiety on prognostic outcomes in patients with HFrEF or unclassified HF with mean LVEF <40%. Our study results lead us to recommend that patients with the HFpEF phenotype should be enrolled into cardiac rehabilitation programs with special attention given to symptoms of anxiety for treatment and be treated with anxiolytic medicine or psychotherapy.

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Disclosures

None.

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