RESEARCH ARTICLE

Sex Differences in Quality of Life and Clinical Outcomes in Patients with Heart Failure

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Abstract

Background: Heart failure (HF) is generally associated with poor quality of life (QoL). Limited data are available characterizing health-related QoL (HRQL) in Chinese patients with HF.

Methods: We used the Minnesota Living with Heart Failure Questionnaire (MLHFQ) to record QoL in 4082 patients with HF from China who were followed up over 12 months in the Heart Failure Registry of Patient Outcomes (HERO) study. Baseline HRQL and differences in QoL between women and men with heart failure were compared. We used multivariable Cox regression with adjustment for variables to assess the association between MLHFQ summary scores and a composite of all-cause mortality and HF hospitalization.

Result: At baseline, the mean MLHFQ in the overall population was 42.9 ± 19.57; the scores for physical and emotional domains were 22.0 ± 8.69 and 8.66 ± 6.08, respectively. Women had a higher (poorer) MLHFQ summary score (44.27 ± 19.13) than men (41.63 ± 19.90) ($P < 0.001$). Female patients also had higher MLHFQ physical and emotional scores than male patients ($P < 0.001$). The specific scores of the questionnaire were higher in women than men. NYHA class was the strongest independent predictor of MLHFQ score ($\beta = 6.12$ unit increment; $P < 0.001$). Sex was not independently associated with higher MLHFQ scores after multivariable adjustments. The 12-month mortality in the overall cohort was 19.6%, the hospitalization rate was 24.4%, and the composite endpoint was 40.15%. A 10-point increase in MLHFQ score was associated with higher risk of mortality (female and male HRs = 1.19 [95% CI 1.12–1.26]; $P < 0.001$ and 1.18 [95% CI 1.12–1.24]; $P < 0.001$, respectively) and composite outcomes (HRs = 1.08 [95% CI 1.04–1.13]; $P < 0.001$ and 1.11 [95% CI 1.07–1.14]; $P < 0.001$, respectively). Females did not show a significant association between HRQL and hospitalization (HR = 1.04 [95% CI 0.99–1.09]; $P = 0.107$).

Conclusion: Quality of life was largely poorer in women than men, but was similar between sexes in terms of physical burden and emotional limitation. HRQL is an independent predictor of all-cause death and HF hospitalization in patients with HF.

Keywords: sex; heart failure; quality of life; mortality; prognosis

Patients with heart failure (HF) have high mortality rates [1]. Given the high prevalence of cardiovascular diseases (including HF) in China, HF has become a critical public health burden [2]. Although a major goal of HF is to improve patient quality of life (QoL) [3], the QoL remains poor in patients with HF [4]. HF has substantial adverse effects on health-related QoL (HRQL) [5–7]. Previous studies have revealed that women with HF have poorer QoL than men with HF [6, 8], and notably have significantly

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higher rates of comorbid depression and anxiety, which may adversely affect their ability to manage the disease [9]. The HRQL has been demonstrated to be a predictor of all-cause death and HF hospitalization across all geographic regions [10]; however, the HRQL and clinical outcomes have not been sufficiently evaluated in China.

In addition to being an important goal for HF treatment, QoL has the potential to serve as a powerful predictor of clinical prognosis in HF. Although some previous studies have reported inconsistent associations between poorer QoL and poorer survival, many studies and trials have demonstrated that HRQL is a predictor of all-cause mortality and HF hospitalization among patients with HF globally [10, 11]. HRQL serves as a marker for predicting major clinical outcomes in patients with HF, and can help clinicians accurately assess patient condition and make appropriate treatment decisions. However, most prior studies have been based on data from Western patients with HF (with prevalence rates of 1%–2%), for whom large amounts of QoL data are available for reference. Insufficient data are available to support and provide a reference for Asian and Chinese patients with HF [12]. Therefore, more specific research on QoL among Chinese patients with HF is imperative to deeper understand the disease differences between genders and potential social and pathophysiological mechanisms, and enable the growing burden of HF disease in China to be effectively addressed.

The Minnesota Living with HF Questionnaire (MLHFQ) is an inexpensive, convenient, and reliable tool to describe the health status of patients with HF [13, 14]. In this study, we used the MLHFQ to (1) examine sex differences in QoL and (2) determine whether the QoL might predict clinical outcomes in HF.

Methods

Study Population

The Heart Failure Registry of Patient Outcomes (HERO) trial [15] is a prospective, longitudinal, seasonally rotating, multicenter registry study that enrolled 5620 patients (50% female) with HF from 73 hospitals in Henan, China, between November 2017 and November 2018, with a previously described design. All patients were ≥18 years of age and had a primary diagnosis of HF. Detailed data were collected, including the patients' sociodemographic characteristics, laboratory test values, diagnostic results, treatments, and clinical outcomes. Prior medical history of hypertension, diabetes, atrial fibrillation, coronary artery disease, or past HF hospitalization was also collected. Diagnosis of HF was based on typical symptoms and signs according to the 2016 European Society of Cardiology HF guidelines, and the clinical diagnosis was validated by a local physician. Patients who died in-hospital or within 3 days after discharge were excluded.

Assessment of HRQOL

The HRQOL was measured with the MLHFQ at baseline for 73% (n=4024) of patients before leaving the hospital. MLHFQ is a hospital-specific, self-administered instrument used to assess the effects of HF, which has been tested and validated [16–20]. The questionnaire contains 21 items with total scores ranging from 0 to 105, with higher scores reflecting a poorer QoL. The Chinese version of the questionnaire has been tested and found to have good reliability and validity in HF [21]. On the basis of the Chinese version of the MLHFQ, two subscales have been identified: a physical subscale consisting of eight items (Q2, Q3, Q4, Q5, Q6, Q7, Q12, and Q13) and an emotional subscale consisting of five items (Q17, Q18, Q19, Q20, and Q21) [21]. The data collectors explained the questionnaire and assisted in its verbal administration to patients before leaving the hospital.

Statistical Analysis

Baseline characteristics of randomized patients were stratified by sex. Categorical variables are expressed as frequencies and percentages, and between-group comparisons were made with chi-square tests or Fisher's exact tests. For continuous variables, the normality of distribution was verified first. If the continuous variables followed a normal distribution, they were expressed as means ± SD, and between-group comparisons were conducted with t-tests. If the continuous variables did not follow a normal distribution, they were expressed as

medians (interquartile ranges), and between-group comparisons were made with Mann-Whitney U nonparametric tests.

Cronbach's alpha was used to assess the internal consistency of MLHFQ domains across sex subgroups, with A≥0.70 indicating reliable consistency [22]. Linear regression was performed to evaluate the MLHFQ total score against independent risk factors, with P<0.1 considered significant. Multivariable Cox proportional hazard models were used to evaluate MLHFQ scores for women and men against 1-year all-cause mortality, HF rehospitalization, and the composite endpoint. Results are reported as hazard ratios and CIs. Kaplan-Meier methods were used to analyze the cumulative incidence rates of all-cause mortality, HF hospitalization, and the composite endpoint in relation to the MLHFQ total score, by using the log-rank test. IBM SPSS statistics version 26.0 and R software version 4.1.3 were used. All tests were two-sided, and P<0.05 was considered significant.

Results

Baseline Characteristics

A total of 4082 patients were included, among whom 2029 (49.8%) were women and 2053 (50.2%) were men. Table 1 describes the baseline characteristics by sex. The female patients' mean (SD) age was 72.9 ± 11.48 years, which was 4 years older than that of male patients (69.1 ± 12.27). Women also had lower BMI and higher systolic blood pressure than men (P<0.001). Regarding lifestyle and social factors, men were more likely to report smoking and alcohol consumption than women (P<0.001). In addition, education and marital status differed significantly between men and women: fewer female than male patients were married, and the men had higher levels of education.

Comorbidities such as hypertension (P=0.002), diabetes, atrial fibrillation, and renal insufficiency (eGFR<60, mL/min/1.73 m^2) were more prevalent in women than men (P<0.001), but the likelihood of having a history of coronary heart disease and COPD was lower in women (P<0.001). Men had a higher prevalence of HFrEF than women (18.1% vs. 10.3%; P<0.001). However, no statistically significant difference in medical treatment was observed between men and women.

Baseline QoL

As shown in Table 1, the mean MLHFQ in the overall population was 42.0 ± 19.57, and the physical and emotional domain scores were 22.0 ± 8.69 and 8.66 ± 6.08, respectively. After adjustment for age and NYHA class, Women had a higher MLHFQ summary score (44.27 ± 19.13) than men (41.63 ± 19.90) (P<0.001). Female patients also had higher MLHFQ physical and emotional scores than male patients (P<0.001).

Internal Consistency of the MLHFQ

As shown in Table 2, in patients with HF and in subgroups based on sex, the degree of internal consistency, evaluated with Cronbach's alpha in each MLHFQ questionnaire domain, was high (α>0.80). Cronbach's alpha coefficient for the MLHFQ questionnaire ranged from a minimum of 0.855 (for the emotional domain) to a maximum of 0.918 (for the total score). This pattern was observed in both female and male patients.

MLHFQ and Associated Factors

Table 3 shows the relationship between MLHFQ scores and independent factors after multivariate adjustment. Female sex was independently associated with higher MLHFQ total scores before adjustment (β=2.42 ± 0.61, P<0.001), but it was no longer a significant predictor after adjustment for demographics, clinical features, social characteristics, log NT-proBNP levels, comorbidities, and medications (β=0.92 ± 0.67, P=0.179). NYHA III/IV class (vs I/II) was the strongest independent predictor of MLHFQ score (β=6.12 ± 0.92, P<0.001). Lower estimated glomerular filtration rate, higher log NT-proBNP levels, and COPD were also independently associated with higher MLHFQ scores. In contrast, higher BMI and higher systolic blood pressure were associated with lower MLHFQ scores (P=0.002). Medications supported by guidelines were associated with lower MLHFQ scores, consistently with improved QoL, but this finding was lacked statistical significance.

Table 1 Baseline Characteristics and Health-Related Quality of Life by Sex.

Characteristics	Overall	Female	Male	P-value
No. of patients	4082	2029	2053	
Demographic and Clinical Characteristics				
Age, y, mean (SD)	70.9 (12.04)	72.9 (11.48)	69.1 (12.27)	<0.001
BMI, kg/m², mean (SD)	23.2 (4.19)	22.9 (3.93)	23.4 (4.43)	<0.001
Systolic blood pressure, mmHg, mean (SD)	134.78 (24.98)	136.42 (25.07)	133.16 (24.91)	<0.001
Heart rate, bpm, mean (SD)	88.49 (22.84)	88.82 (23.68)	88.16 (22.01)	0.36
eGFR<60, mL/min/1.73, n (%)	1032 (25.3)	603 (29.7)	429 (20.9)	<0.001
NYHA class III/IV, n (%)	1911 (46.8)	961 (47.4)	950 (46.3)	0.505
Ejection fraction<40%, n (%)	581 (14.2)	209 (10.3)	372 (18.1)	<0.001
Smoking(any), n (%)	986 (24.2)	33 (1.6)	953 (46.4)	<0.001
Alcohol(any), n (%)	649 (15.9)	16 (0.7)	633 (30.8)	<0.001
Social characteristics				
Insurance, n (%)	3821 (93.6)	1905 (93.9)	1916 (93.3)	0.503
Marital status, n (%)				<0.001
Married	3531 (86.5)	1684 (83.4)	1847 (90.3)	
Widowed/divorced/separated/others	476 (11.7)	332 (16.4)	144 (7.0)	
Single	57 (0.1)	3 (0.1)	54 (2.6)	
Education				<0.001
College graduates	56	8 (0.4)	48 (2.3)	
Middle school	740	213 (10.5)	527 (25.7)	
Elementary school and below	2813	1581 (77.9)	1232 (60.0)	
Unknown	473	227 (11.2)	246 (12.0)	
Laboratory				
Hemoglobin, g/L, mean (SD)	123.52 (22.24)	118.00 (20.08)	128.95 (22.93)	<0.001
NT-proBNP, ng/L, mean (SD)	5665.61 (7180.45)	5471.28 (7226.06)	5860.83 (7132.27)	0.201
Glycated hemoglobin; HBALC, %, mean (SD)	6.38 (1.65)	6.47 (1.68)	6.27 (1.61)	0.019
Medical Past, n (%)				
Diabetes mellitus	798 (19.5)	456 (22.5)	342 (16.7)	<0.001
Hypertension	1936 (47.4)	1019 (50.2)	917 (44.7)	0.002
Atrial fibrillation	1063 (26.0)	577 (28.4)	486 (23.7)	0.002
Coronary artery disease	738 (18.1)	280 (13.8)	458 (22.4)	<0.001
COPD, n (%)	377 (9.2)	128 (6.3)	249 (12.1)	<0.001
Medical treatment, n (%)				
Beta-blocker	2082 (51.0)	1034 (51.0)	1048 (51.0)	0.979
ACEI	937 (23.0)	444 (21.9)	493 (24.0)	0.249
ARB	850 (20.8)	421 (20.7)	429 (20.9)	0.721
ARNI	29 (0.7)	10 (0.5)	19 (0.9)	0.201
MRA	2898 (71.0)	1413 (69.6)	1485 (72.3)	0.161
Diuretics	2398 (58.7)	1183 (58.3)	1215 (59.2)	0.825
Digoxin	874 (21.4)	396 (19.5)	478 (23.3)	0.013
Health-related quality of life, mean (SD)				
MLHFQ summary score (0–105)	42.9 (19.57)	44.27 (19.13)	41.63 (19.90)	<0.001
MLHFQ physical limitation score (0–40)	22.0 (8.69)	22.58 (8.46)	21.44 (8.88)	<0.001
MLHFQ emotional score (0–25)	8.66 (6.08)	9.05 (6.00)	8.29 (6.13)	<0.001

Table 2   Internal Consistency of the MLHFQ Domains.

	Total patients	Female	Male
Total score	0.918	0.914	0.921
Physical score	0.882	0.880	0.883
Emotional score	0.855	0.861	0.847

Table 3   Relationship of MLHFQ Scores and Independent Factors.

	MLHFQ total score		
	Beta	SE	P-value
Sex, Female[1]	2.42	0.61	<0.001
Sex, Female[2]	0.92	0.67	0.179
Age	0.02	0.03	0.469
BMI	−0.24	0.08	0.002
SBP>140 mmHg	−0.10	0.03	0.002
bpm>100 bpm	0.03	0.05	0.532
eGFR<60 mL/min/1.73 m^2	5.48	0.67	<0.001
NYHA III/IV versus I/II	6.12	0.92	<0.001
Education (Middle school)	−3.25	0.85	<0.001
Insurance	1.38	0.84	0.104
Diabetes mellitus	1.24	0.85	1.463
Hypertension	−0.76	0.71	0.287
Atrial fibrillation	1.167	0.76	0.125
COPD	2.63	1.16	0.003
Coronary artery disease	0.035	0.719	0.961
Log NT-proBNP	4.20	0.55	<0.001
ACEI/ARB/ARNI	−0.01	0.681	0.989
B-blocker	−1.077	0.681	0.114
MRA	−0.679	0.898	0.450
Diuretics	−0.432	0.798	0.588
Digoxin	0.072	0.828	0.930

Note: Adjusted for listed variables for the P<0.1. Female[1] was Single factor analysis; Female[2] was adjusted for demographics, clinical features, social characteristics, log NT-proBNP levels, comorbidities, and medication.

MLHFQ and Clinical Outcomes

During the 12-month follow-up period, a total of 789 patients (19.6%) died, 982 (24.4%) were readmitted because of HF, and 1617 (40.2%) experienced either death or readmission. As shown in Figure 1, the mortality rate was positively associated with MLHFQ scores. Similar relationships were observed for the composite endpoint of all-cause mortality or HF readmission. Kaplan-Meier analysis indicated that the incidence of both mortality and the composite endpoint was significantly associated with MLHFQ score (log-rank, P<0.001).

Multivariate analyses of the relationships of sex with the mortality rate, readmission rate, and composite endpoint are presented in Figure 2. The MLHFQ total score was a strong independent predictor of clinical outcomes. Poor health-associated QoL (higher MLHFQ scores) was significantly associated with a higher risk of clinical outcomes, including mortality (with a hazard ratio [HR=1.19 [95% CI 1.12–1.26] for women and 1.18 [95% CI 1.12–1.24] for men per 10-point increase in MLHFQ score, P<0.001) and composite endpoint (with an HR of 1.08 [95% CI 1.04–1.13] for women and 1.11 [95% CI 1.07–1.14] for men, P<0.001). No significant association was observed between HRQL and readmission outcomes in women (HR=1.04[95% CI 0.99–1.09]; P=0.107), whereas men still showed a positive correlation (HR=1.07[95% CI 1.02–1.11]; P=0.002). However, no significant difference was observed in the predictive ability of MLHFQ between men and women for all-cause mortality, readmission, or composite endpoint (interaction P>0.5).

Discussion

This retrospective study, based on the HERO cohort, was aimed at evaluating and studying the basic characteristics, QoL, mortality, and readmission rates among Chinese patients with HF, and to assess sex differences. The study also investigated the differences in QoL between male and female patients with HF, and the associations of MLHFQ scores with outcomes such as mortality and HF readmission rates. On the basis of the baseline characteristics of the patients, the following findings were discovered: (1) female patients with HF were older and had a higher proportion of NYHA functional class III/IV than male patients; (2) although both sexes had equal medical insurance and drug therapy, women had lower levels of education than men, and a significantly higher proportion of women than men were divorced or widowed; (3) after adjustment for age and heart function
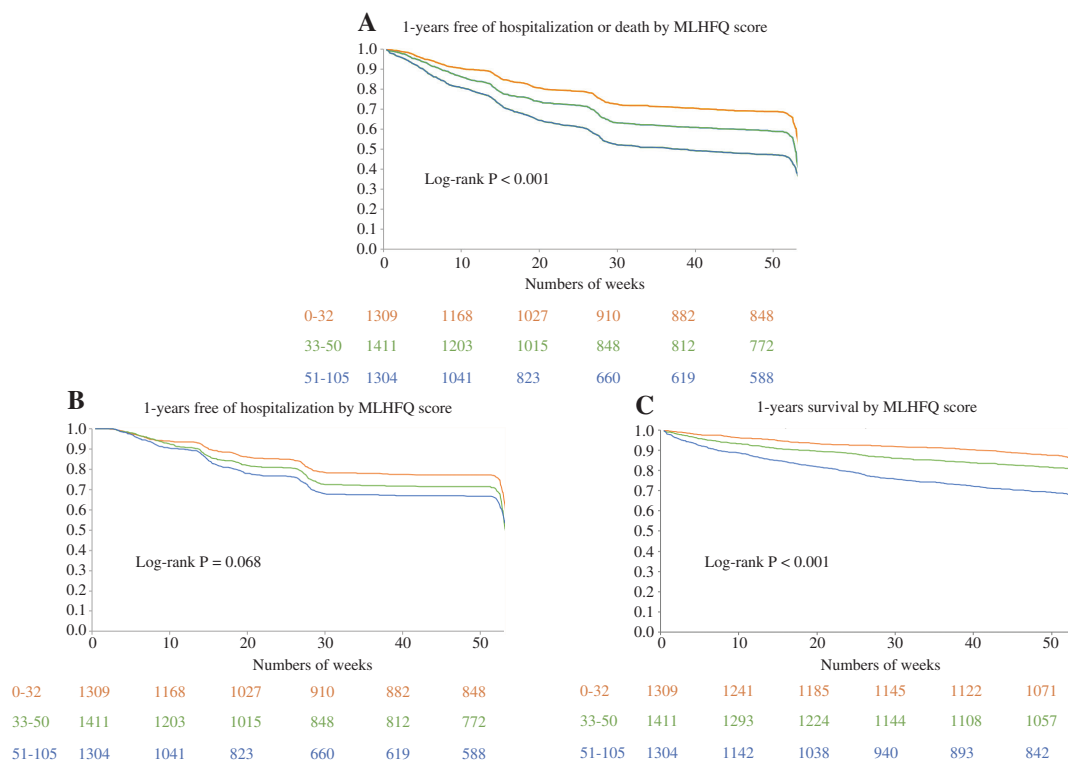
A 1-years free of hospitalization or death by MLHFQ score

0-32	1309	1168	1027	910	882	848
33-50	1411	1203	1015	848	812	772
51-105	1304	1041	823	660	619	588

B 1-years free of hospitalization by MLHFQ score   **C** 1-years survival by MLHFQ score

0-32	1309	1168	1027	910	882	848	0-32	1309	1241	1185	1145	1122	1071
33-50	1411	1203	1015	848	812	772	33-50	1411	1293	1224	1144	1108	1057
51-105	1304	1041	823	660	619	588	51-105	1304	1142	1038	940	893	842

Figure 1 Clinical Outcomes by MLHFQ Category.
Kaplan-Meier curves for all-cause mortality or HF hospitalization (A), HF hospitalization (B), and all-cause mortality (C). MLHFQ category ranges are 0–32, 33–50, and 51–105, with higher scores indicating poorer health-associated QoL.

Subgroups	HR (95% CI)	P value
All−cause mortality		
Female	1.19 (1.12 to 1.26)	<0.001
Male	1.18 (1.12 to 1.24)	<0.001
HF hospitalization		
Female	1.04 (0.99 to 1.09)	0.107
Male	1.07 (1.02 to 1.11)	0.002
All−cause mortality or HF hospitalization		
Female	1.08 (1.04 to 1.13)	<0.001
Male	1.11 (1.07 to 1.14)	<0.001

Figure 2 Association of QoL with 1-year All-cause Mortality.
Adjusted for age, BMI, systolic blood pressure, heart rate, eGFR, log NT-proBNP, diabetes, hypertension, COPD, ACE inhibitors/ARB, β-blockers, diuretics, and digoxin.

classification, female patients with HF had a heavier symptom burden and more emotional problems than male patients at baseline; however, after multivariate adjustment, sex was no longer an independent factor influencing QoL; and (4) after the same standardized treatment, the mortality and HF readmission rates were similar between female and male patients. Overall, differences in QoL between female and male patients with HF might not have been directly due to female sex.

Sex Differences in QoL with Patients with HF

Previous studies have shown that, despite receiving optimal medication therapy, women remain more likely than men to experience symptoms of

HF and to have poorer QoL [23]. For example, in a secondary analysis of the CHARM study, women have been found to have progressively increasing symptoms, including dyspnea at rest and on exertion, and more severe peripheral edema [24]. The PAL-HF study also demonstrated that women had significantly lower baseline QoL scores than men, as measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Functional Assessment of Chronic Illness Therapy-Palliative Care scale (FACIT-Pal) [25]. This study further supports these previous findings by showing that women with HF in China have poorer QoL than men.

Although previous studies have confirmed poorer QoL in women than men with HF, the reasons for the disparity between men and women might not be associated with sex itself, but instead might be due to other underlying factors that differ between sexes. In this study, these potential factors included lower levels of education, as well as being divorced or widowed, all of which were identified as strong independent predictors of QoL in the multifactorial analysis. The PAL-HF study has shown that social and economic factors may lead to higher levels of depression and anxiety in women than men [25], thereby directly or indirectly increasing disease burden, both physically and mentally, and ultimately decreasing QoL among women.

Notably, female patients in the cohort were generally older, and had poorer heart function and higher NT-proBNP levels. Despite adjustment for these factors that significantly differed between sexes, a significant difference in QoL remained. Further exploration will be important to determine why women choose to seek medical attention only when their symptoms are more severe, or when their state of HF is poorer. Moreover, earlier, more timely attention must be paid to changes in the condition and QoL of female patients with HF.

In this study, given that both sexes received the same standard treatment, we believe that differences in QoL might have been due to different social situations between sexes. Among Chinese patients with HF, women had lower education levels, and were more likely to be single and to seek medical care later than men. Clinically, paying greater attention to the personal and social status of female patient groups, rather than focusing on the sex factor itself may be key to improving QoL.

Prognostic Utility of QoL

Numerous studies have demonstrated the ability of HRQL to predict mortality and readmission rates in patients with HF, but most of the data have come from Western countries [26–30]. However, HRQL outside of Western countries has also been demonstrated to be an independent predictor of all-cause mortality in HF, in studies such as ACTION-HF (n=1990); ASIAN-HF (n=3688), which performed a multi-ethnic comparison; the SHOP study (n=1070) from multiple countries in Southeast Asia (China, Malaysia, and India); and the G-CHF study (n=23291) in patients with HF worldwide [10, 31, 32]. Higher level evidence provided by meta-analyses has also indicated similar results. One meta-analysis of 24 studies has demonstrated that every 10-point increase in MLHFQ score increases the risk of all-cause mortality by 12% (95% CI 6%–18%), and higher MLHFQ scores at admission, defined by a lower QoL, are associated with increased risk of all-cause mortality in patients with HF [11]. These findings are consistent with our study results, which indicated that, even after adjustment for factors associated with physical signs and known factors affecting HF prognosis, QoL remained a predictor of mortality and readmission rates in both female and male patients with HF.

To our knowledge, patient QoL is not regularly evaluated during admission assessments in clinical practice. Nevertheless, these research findings suggest that QoL assessment tools, such as MLHFQ, could have a greater role in clinical practice. Quantifying QoL scores is a straightforward yet powerful predictor, which is rapid, convenient, and inexpensive, and can be used in most primary and clinical settings to better stratify risk among new patients with HF at admission. These research findings support the incorporation of QoL assessment as a crucial monitoring indicator in future clinical trials and registry cohorts associated with HF.

We did not observe a significant sex difference in the relationship between QoL and HF prognosis, but similar predictive values were found in both males and females. However, unmeasured biases and unconsidered influencing factors might have interfered with the results. At the sociological level, race and sex biases have important roles in QoL, as evidenced by the literature on health inequalities based on race and

sex [33]. At the individual level, factors such as negative emotions, cultural factors, and personality traits can also affect patients' perceptions [34].

Limitations

First, because our study was retrospective, information on unmeasured confounding variables such as patient mental state and psychological factors such as anxiety, depression, and cognitive impairment, which are known to be important factors affecting QoL, were not available [35]. For laboratory tests and examinations, we chose indicators commonly used in routine clinical practice, which were unlikely to have been affected by missing data; however, some strong predictors might have been be missed [36]. In addition, given the potentially lower social status, income, and education levels among the women than the men in this study, we might have missed data on the complete socio-economic status of the patients and possibly on the effects of sex bias on QoL. These aspects must be further researched and explored. Although QoL is a treatment goal for HF, we did not follow up on patient QoL scores; therefore, how QoL changes under standard treatment is unclear and requires further research, particularly given that reasonable exercise therapy has been found to improve QoL [37].

Conclusion

In the HERO cohort of patients with HF, female patients had significantly lower QoL scores than male patients, but sex itself was not an independent predictor of QoL. Further research is needed to clarify and improve QoL among female patients with HF, including investigation of their socioeconomic status. Both lower HRQL was strong independent predictors of all-cause mortality and HF readmission. Therefore, assessment of QoL is valuable in the evaluation of patients with HF at admission.

Data Availability Statement

The article used data obtained from the HERO database.(ChiCTR.org.cn(ChiCTR1800014786)).

Ethics Statement

It was approved centrally by the Ethics Committee on Scientific Research and Clinical Trials at the First Affiliated Hospital of Zhengzhou University (in September 2017; approval number 2014SY-079) and by the local health research ethics board at each participating hospital.

Author Contributions

LJX and DJZ conceived the study. LJX and ZL acquired the data. LJX, WXS and ZL analyzed the data. LJX reviewed the literature and prepared the first draft of this manuscript. ZL and DJZ critically reviewed and edited the manuscript, and approved the final version. All authors have read and approved the final manuscript.

Acknowledgments

Conflict of Interest

There are no conflicts of interest.

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