

Sex Differences in Patients with Heart Failure with Reduced Ejection Fraction Combined with Anemia and Hyperuricemia: A Retrospective Case Study

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Objective: Heart failure with reduced ejection fraction (HFrEF) is associated with high mortality and morbidity. This study aimed to investigate sex differences in clinical characteristics, ventricular remodeling, cardiovascular risk factors, and prognosis among patients with HFrEF complicated by anemia and hyperuricemia.

Subjects and Methods: We analyzed data from patients with HFrEF admitted to the Affiliated Hospital of Youjiang Medical University for Nationalities between January 1, 2018, and September 1, 2022. A total of 185 patients with HFrEF, anemia, and hyperuricemia (HU) were included. Laboratory and echocardiographic parameters were examined, and Cox regression analysis was used to identify prognostic risk factors. Clinical characteristics and prognostic factors were compared between sexes.

Results: Female patients had lower body weight, smaller body size, more severe anemia, and fewer ischemic causes of ventricular remodeling compared with male patients. Male patients had a higher prevalence of smoking and renal insufficiency. Serum uric acid predicted lower extremity venous thrombosis (area under the curve = 0.736). During a median follow-up of 21.78 months, no significant sex difference in cardiovascular events was observed. However, multivariate Cox proportional hazards analysis demonstrated sex-specific prognostic factors. The independent risk factors in males were body weight (HR = 1.035, 95% CI: 1.016–1.054, $P = 0.001$), total protein (HR = 0.965, 95% CI: 0.934–0.997, $P = 0.031$), albumin/globulin ratio (HR = 2.024, 95% CI: 1.093–3.749, $P = 0.025$), and atrial fibrillation (HR = 0.399, 95% CI: 0.254–0.627, $P = 0.001$). Independent risk factor in females was MCHC (HR = 1.037, 95% CI: 1.011–1.064, $P = 0.005$).

Conclusion: In patients with HFrEF, anemia, and HU, males and females exhibited distinct clinical characteristics and cardiovascular risk factors, despite having similar survival outcomes. These findings underscore the importance of addressing sex-specific risk profiles in the clinical management of HFrEF.

Keywords: chronic heart failure, anemia, serum uric acid, ventricular remodeling, sex differences

Introduction

Heart failure (HF) is a multifaceted clinical syndrome caused by diminished cardiac function, which restricts the heart's capacity to meet the body's metabolic requirements.¹ Despite being a significant global health issue, HF significantly contributes to both morbidity and mortality. Heart failure with reduced ejection fraction (HFrEF) is a subtype of HF, and its prevalence increases with age. Furthermore, the 5-year post-discharge survival rate for patients with HFrEF is only 25%.² Epidemiological studies indicate that the lifetime risk of developing HF is nearly equivalent for both sexes. However, men are more predisposed to developing HFrEF among HF subtypes, whereas women are predominantly



impacted by HF with preserved EF.³ Significant differences exist between men and women in clinical manifestations, risk factors, and long-term outcomes associated with HFrEF.⁴

Anemia and iron deficiency are prevalent in patients with HF and are associated with more severe symptoms and outcomes. Anemia is defined as a hemoglobin level <12 g/dL in women and <13 g/dL in men. The prevalence of anemia and iron deficiency is significantly higher in female patients with HF.⁵ Furthermore, hyperuricemia (HU) is associated with acute HF events and poor outcomes in HF, with a sex-specific relationship between serum uric acid (SUA) levels and long-term prognosis for HF. Specifically, SUA is an independent predictor of long-term prognosis in male patients with HF, but it does not hold the same predictive value in female patients.^{6,7}

Anemia and HU have evident sex disparities in HFrEF and are associated with more severe symptoms and outcomes. Therefore, this study investigated the sex-specific clinical characteristics, examination findings, and prognostic relevance of anemia and HU in patients with HFrEF.

Subjects and Methods

Study Subjects

A retrospective analysis was conducted with 185 patients with HFrEF, anemia, and HU who were hospitalized in the Department of Cardiovascular Medicine at the Affiliated Hospital of Youjiang Medical University for Nationalities from January 1, 2018, to September 1, 2022.

Inclusion Criteria

(1) all subjects met the diagnostic criteria for HFrEF as per the European Society of Cardiology guidelines;⁸ (2) left ventricular EF (LVEF) <40% and elevated N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels; and (3) aged 18–85 years.

Exclusion Criteria

(1) subjects using xanthine oxidase inhibitors, uric acid-lowering drugs, and colchicine; (2) those with hyperthyroidism; (3) those with multiple organ failure; (4) those with concurrent malignant tumors; (5) those with infectious diseases, such as tuberculosis; (6) those with severe mental illness; (7) those with a history of major surgical treatment; and (8) those with severe liver dysfunction and renal insufficiency or long-term dialysis treatment for renal failure.

Criteria of Diagnosis

Anemia was diagnosed using the World Health Organization criteria: hemoglobin concentration <120 g/L in non-pregnant adult women or <130 g/L in adult men. The diagnostic criteria for hyperuricemia were adult blood uric acid levels >420 $\mu\text{mol/L}$ on two non-consecutive fasting occasions, regardless of sex, and under a normal purine diet. These diagnostic standards were derived from the China Multi-disciplinary Expert Consensus on the Diagnosis and Treatment of Hyperuricemia and Related Diseases (2023 Edition).

Echocardiographic Findings and Laboratory Data

All inpatients underwent echocardiography. Detailed measurements were recorded, including aortic root diameter (AO), left atrial diameter (LAS), interventricular septal thickness (IVSD), left ventricular end-diastolic diameter (LVDD), left ventricular end-systolic diameter (LVDS), left ventricular posterior wall thickness (LVPWD), left ventricular end-systolic diameter (LVS), and EF. Laboratory evaluations included complete blood count, coagulation profile, liver and kidney function tests, lipid profile, myocardial enzymes, thyroid function, and NT-pro-BNP levels.

Baseline demographic data, clinical characteristics, laboratory results, and medication use were retrieved from hospital records. Patients with HFrEF, anemia, and HU who met the inclusion criteria (and did not meet exclusion criteria) were divided into male ($n = 128$) and female ($n = 57$) groups. All medical data were fully protected, and personal data were anonymized and coded with randomly generated numbers.

Cardiovascular Prognostic Indicators

The primary endpoint was hospitalization for HF, incidence of cardiovascular diseases (acute myocardial infarction, stroke), and all-cause mortality. Follow-up data for all subjects were retrospectively collected by reviewing electronic medical records or through telephone interviews until any endpoint was reached or until the review date of January 31, 2024. The follow-up duration was calculated from the date of discharge to the occurrence of any endpoint event or the last follow-up date.

Statistical Methods

Statistical analyses were performed using SPSS (IBM SPSS, Inc., Armonk, New York, USA) and Prism (GraphPad Software, Inc., San Diego, California, USA). Continuous variables were analyzed using the Shapiro–Wilk test to assess normality. Normally distributed data were expressed as mean \pm standard deviation, and comparisons between groups were performed using Student's *t*-test. Continuous data for male and female populations were analyzed using the Wilcoxon–Mann–Whitney test, while categorical data were expressed as percentages and analyzed using the χ^2 test or Fisher's exact test to evaluate differences. The diagnostic value of SUA and NT-pro-BNP in predicting the development of lower extremity venous thrombosis was determined using receiving operator characteristic (ROC) curve analysis. Kaplan–Meier survival analysis was employed to assess the long-term outcomes between sexes, and comparisons of the results were performed using the Log rank test. Univariate analysis ($P \leq 0.1$) was performed on relevant variables to identify cardiovascular risk factors in patients with HFrEF, anemia, and HU, with significant variables analyzed in a subsequent multivariate Cox regression analysis to determine independent predictors associated with adverse outcomes. A two-sided $P < 0.05$ was considered statistically significant.

Results

Comparison of General Clinical Data at Admission Between Male and Female Patients

Between January 2018 and September 2022, a total of 1140 patients with HFrEF were screened at our center. Of these, 936 patients were excluded according to predefined criteria, and 19 were excluded owing to missing laboratory data. Ultimately, 185 patients were enrolled: 128 men (69.2%) and 57 women (30.8%). No significant difference was found in the mean age between male and female patients, with both groups consisting primarily of elderly individuals. The female patients tended to be leaner and had lower body weights ($P < 0.05$), while coronary heart disease and smoking were more prevalent among the male patients ($P < 0.05$). No significant differences were observed between the two groups in terms of age, length of hospital stay, body mass index, vital signs, New York Heart Association classification, or other comorbid conditions ($P > 0.05$; Table 1).

Table 1 Baseline Characteristics of Male and Female Patients

Variable	Female (n = 57)	Male (n = 128)	t/Z/ χ^2	P
Mean age (years)	72.02 \pm 8.73	70.61 \pm 9.31	0.992	0.323
Mean weight (kg)	50.83 \pm 8.01	58.67 \pm 9.64	-5.763	0.000
Mean BMI (kg/m ²)	23.15 \pm 3.15	24.37 \pm 3.43	0.304	0.776
Hospital stay (days)	6.60 \pm 3.02	7.34 \pm 4.11	-1.367	0.174
Pulse rate (bpm)	83.97 \pm 17.11	89.59 \pm 19.91	-1.960	0.052
Systolic blood pressure (mmHg)	131.89 \pm 23.39	132.45 \pm 27.25	-1.05	0.292
Systolic blood pressure (mmHg)	79.42 \pm 15.87	81.24 \pm 15.48	-0.726	0.469
Heart rate (bpm)	87.51 \pm 20.72	93.44 \pm 22.48	-1.750	0.083
Smoker	2 (0.01)	91 (49.2)	85.19	0.000
Comorbidities				
Coronary heart disease	25 (13.5)	79 (42.7)	6.978	0.011
Hypertension	30 (16.2)	78 (42.2)	1.561	0.229

(Continued)

Table 1 (Continued).

Variable	Female (n = 57)	Male (n = 128)	t/Z/ χ^2	P
Atrial fibrillation	16 (8.7%)	27 (14.6)	1.195	0.286
Valvular heart disease	23 (12.4)	60 (32.4)	0.805	0.383
Cardiomyopathy	30 (16.2)	61 (32.9)	0.520	0.488
Diabetes mellitus	24 (12.9)	27 (14.6)	0.998	0.364
Renal insufficiency	35 (18.9)	74 (40)	0.300	0.588
Thrombosis of the deep leg veins	7 (3.8)	7 (3.8)	2.767	0.134
NYHA classification				
II	18 (9.7)	31 (16.8)	3.031	0.220
III	21 (11.4)	63 (39.5)		
IV	20 (10.8)	34 (12.9)		

Table 2 Comparison of Blood Routine Indicators Between Male and Female Patients

Variable	Female (57)	Male (128)	t/Z	P
White blood cell count ($\times 10^9/L$)	7.25 \pm 2.87	8.30 \pm 3.17	-2.234	0.027
Absolute monocyte count ($\times 10^9/L$)	0.44 \pm 0.17	0.57 \pm 0.25	-4.175	0.000
Red blood cell count ($\times 10^{12}/L$)	3.65 \pm 0.64	3.95 \pm 0.68	-2.908	0.004
Hemoglobin (g/L)	98.11 \pm 14.20	109.40 \pm 15.48	-4.855	0.000
Hematocrit (L/L)	0.31 \pm 0.04	0.34 \pm 0.04	-4.356	0.000
Mean corpuscular hemoglobin concentration (g/L)	313.32 \pm 11.06	318.30 \pm 13.14	-2.665	0.009

Comparison of Routine Blood Test Indicators at Admission Between Male and Female Patients

Sex differences were observed in routine blood tests, including white blood cell count, hemoglobin level, absolute monocyte count, red blood cell hematocrit, and mean corpuscular hemoglobin concentration. Specifically, women exhibited significantly lower levels of these indicators than men ($P < 0.05$ or $P < 0.01$), with the most pronounced difference observed in the absolute monocyte count (MON#; $P < 0.000$). These findings indicate a higher prevalence of anemia among women (Table 2).

Comparison of Laboratory Indicators Between Male and Female Patients

Sex differences were observed in total protein, globulin, albumin/globulin ratio, and L- γ -glutamyltransferase. Male patients had a significantly higher prevalence of hypoalbuminemia and poorer glomerular filtration rates ($P < 0.05$ or $P < 0.01$). No sex differences were noted in other laboratory parameters, such as SUA or NT-pro-BNP ($P > 0.05$; Table 3).

Table 3 Comparison of Experimental Indicators Between Male and Female Patients

Variable	Female (57)	Male (128)	t/Z	P
TP (g/L)	66.06 \pm 6.48	63.95 \pm 5.89	2.101	0.038
LDH (U/L)	269.91 \pm 13.98	235.68 \pm 7.73	2.148	0.034
L- γ -GGT (U/L)	41.22 \pm 3.86	63.13 \pm 6.47	-2.910	0.004
eGFR (mL/min/1.73 m ²)	41.29 \pm 20.86	52.10 \pm 24.01	-3.102	0.002
GLB (g/L)	29.25 \pm 5.99	27.19 \pm 5.30	2.233	0.028
ALB/GLB (g/L)	1.29 \pm 0.33	1.39 \pm 0.31	-2.083	0.040

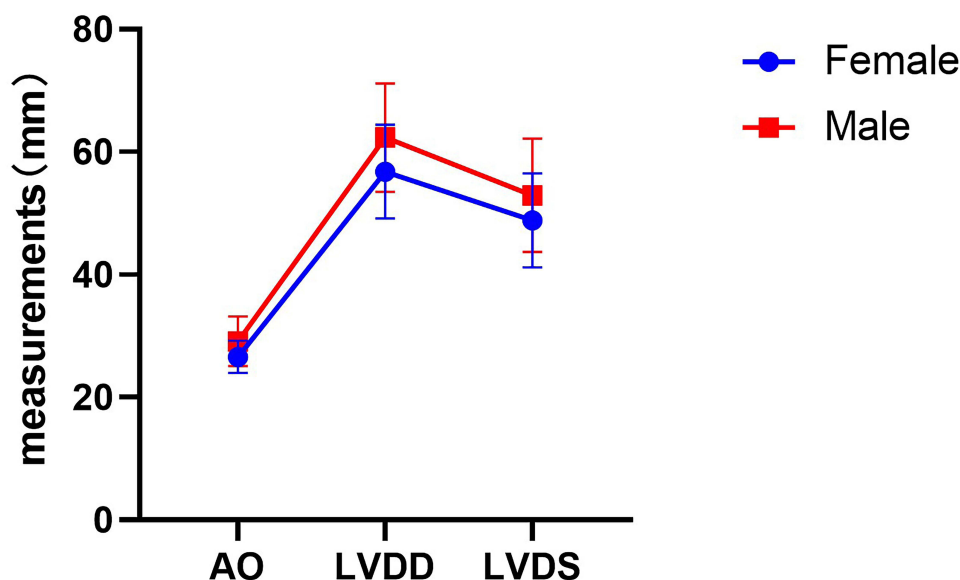


Figure 1 Comparison of echocardiographic parameters between male and female patients.

Comparison of Echocardiographic Parameters Between Male and Female Patients

Echocardiographic parameters reflecting LV remodeling, such as aortic root diameter (AO), LVDD, and LV systolic dysfunction (LVDS), were significantly lower in female patients than in male patients ($P < 0.01$). However, no sex differences were observed in LVEF, fractional shortening, or other related parameters ($P > 0.05$). These findings demonstrate sex-specific differences in the influence of ventricular remodeling on cardiac function (Figure 1).

Predictive Value of SUA and NT-Pro-BNP for Lower Extremity Venous Thrombosis

The ROC curve analysis for both sexes revealed that the area under the curve (AUC) for SUA was 0.736, while the AUC for NT-pro-BNP was 0.678 (Table 4 and Figure 2). These findings indicate that SUA has a superior diagnostic value for predicting the formation of lower extremity venous thrombosis compared to NT-pro-BNP.

Cardiovascular Prognostic Outcomes Between Male and Female Patients

During the median follow-up period of 21.78 (interquartile range: 19.42, 24.14) months, 181 patients (99.5%) experienced at least one confirmed adverse outcome, of which 118 (63.8%) were hospitalized due to HF progression, 24 (13%) died, and 38 (20.5%) experienced cardiovascular events. Kaplan–Meier survival analysis revealed no significant difference in overall survival rates between female and male patients (Log rank test, $P = 0.407$; Figure 3).

Univariate analysis of variables in Tables 1–3 was performed, and those with significant differences were included in both univariate and multivariate Cox regression analyses. Sex-specific differences in prognostic risk factors were observed. The independent risk factors for men included body weight, total protein level, albumin/globulin ratio, and atrial fibrillation ($P < 0.05$ or $P < 0.01$), whereas the independent risk factor for women was mean corpuscular hemoglobin count (Table 5). These differences may be attributed to sex-specific physiological and pathological mechanisms.

Table 4 Predictive Value of SUA and NT-Pro-BNP for Lower Extremity Venous Thrombosis

Project	Area Under the Curve (95% CI)	Sensitivity %	Specificity %	Optimal Critical Value	P
SUA ($\mu\text{mol/L}$)	0.736 (CI: 0.606–0.866)	92.9	73.7	486	0.003
NT-pro-BNP (pg/mL)	0.678 (CI: 0.562–0.794)	85.7	42.7	11,261.5	0.027

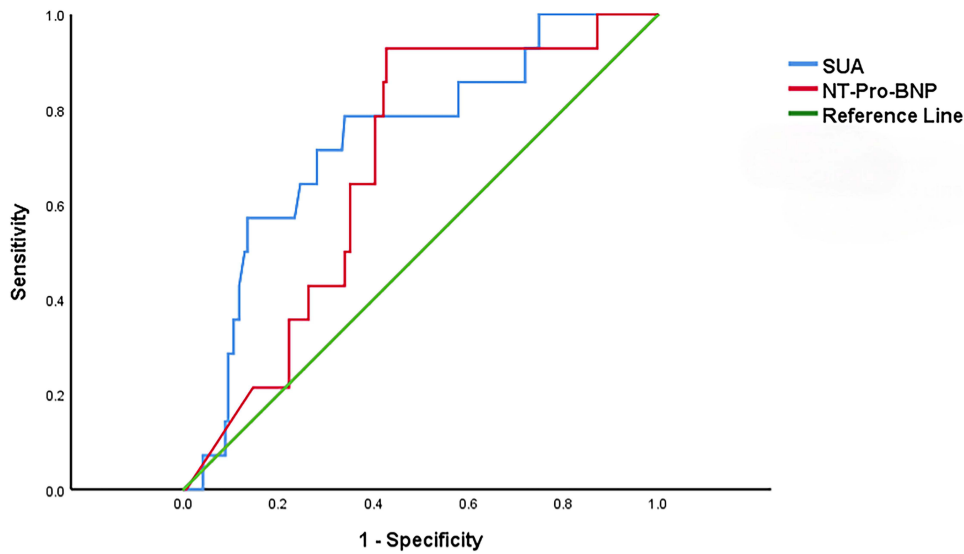
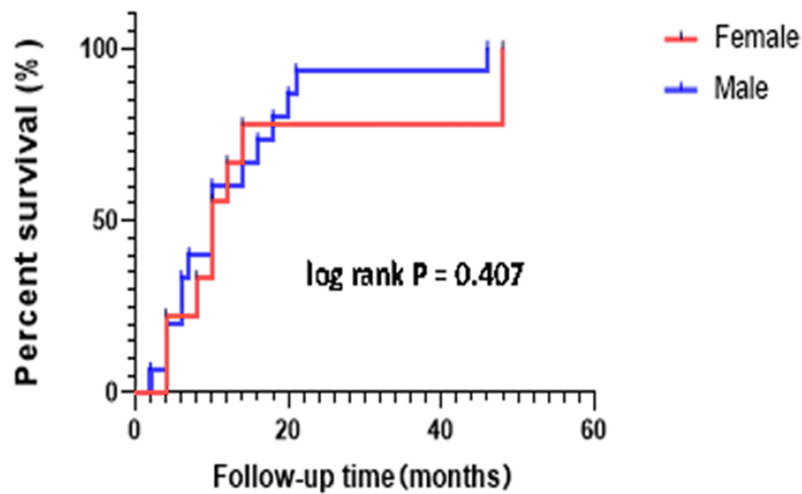


Figure 2 Predictive value of SUA and NT-pro-BNP for lower extremity venous thrombosis.



Subjects at risks

Male	128	56	38	26
Female	57	36	11	10

Figure 3 Kaplan–Meier survival curve analysis for male and female patients.

Discussion

This study shows patients with HF_{rEF} with concurrent anemia and HU and elucidated several sex-specific differences: 1) The proportion of women in the study cohort was lower. Compared with the men, women had a leaner physique and lower body weight and exhibited a higher prevalence of anemia and nutritional status; 2) Women were less likely to have ischemic causes and had other various cardiovascular risk factors, which aligns with previous research;⁹ 3) Despite the absence of differences between the sexes in overall survival, the independent risk factors varied by sex. Specifically, body weight, nutritional status, and atrial fibrillation were independent risk factors for prognosis in men.

Anemia is common in patients with HF, with a prevalence of 14%–61%. Furthermore, it is an independent prognostic factor for HF and is associated with adverse outcomes.^{10–13} The incidence of anemia in female patients with HF is higher

Table 5 Cox Proportional Hazards Regression Model Identifying Variables Associated with Cardiovascular Outcomes in Males and Females

	Univariable Analysis HR (95% CI)	P	Multivariable Analysis HR (95% CI)	P
MCHC (Female)	1.036 (1.010, 1.063)	0.006	1.037 (1.011, 1.064)	0.005
Weight (Male)	1.032 (1.013, 1.05)	0.001	1.035 (1.016, 1.054)	0.000
TP (Male)	0.965 (0.934, 0.997)	0.031	0.952 (0.925, 0.979)	0.001
ALB/GLB (Male)	2.065 (1.037, 4.112)	0.039	2.0249 (1.093, 3.749)	0.025
Atrial fibrillation (Male)	0.444 (0.286, 0.688)	0.000	0.399 (0.254, 0.627)	0.000

than that in male patients. HU is common in patients with HF, is a risk factor for HF, is associated with more advanced disease, and is a strong and independent predictor of adverse outcomes in HF.^{14–17} We found that anemia was more severe in women and was associated with adverse outcomes in HF. However, women showed better renal function and nutritional status than men, indicating that the impact of HF on liver and kidney function is better in women. Men exhibited a higher prevalence of hypoalbuminemia and more symptoms and signs of HF (such as edema and congestion). Thus, corrective treatment for HF (eg, diuretic therapy) would be more challenging in male patients. Elevated UA levels may contribute to HF-related echocardiographic abnormalities by affecting endothelial function and inflammatory responses.¹⁸ Women showed specific tendencies in valvular structural changes, ie, smaller LV size and volume, and were more prone to concentric ventricular remodeling. These phenomena may be attributed to the extent of LV structural damage caused by underlying intracellular and molecular processes and thus indicate sex-specific differences in pathological LV remodeling.¹⁸

In this study, all patients were admitted due to acute exacerbation of their condition, with most heart function classifications between III and IV. Sex-based differences were observed in the history of underlying diseases, with smoking being a more common etiological factor in men. The relatively lower smoking rate among Chinese women than in men reflects some cultural and customary differences between the sexes. Smoking in men has become a major risk factor for coronary artery atherosclerosis (CAD). HF caused by coronary heart disease is more common in men with a poor prognosis.¹⁹ Furthermore, while female patients with CAD have a higher burden of coronary heart disease, the degree of CAD obstruction is lower, or the incidence of ischemia without obstructed coronary arteries on coronary angiography is higher, which may be related to the lower degree of CAD. However, no sex differences were observed in cardiovascular death or myocardial infarction.^{20–22}

Elevated SUA levels are common in HF and are considered markers of tissue oxidative stress and inflammation. The onset and persistence of atrial fibrillation may be closely related to inflammation and oxidative stress.^{23,24} A significant correlation between UA and atrial fibrillation has been observed in both sexes. In particular, elevated UA levels are associated with an increased risk of atrial fibrillation in women.^{25,26} The current study identified atrial fibrillation as an independent risk factor for prognosis assessment in men, which may indicate the role of SUA in mediating inflammation and oxidative stress. Furthermore, our study found that HU is a diagnostic marker for lower extremity venous thrombosis and a high-risk factor for venous thromboembolism (VTE), alongside atrial fibrillation. Most observational clinical studies have reported a positive correlation between SUA and thrombosis risk,^{27–31} possibly involving the inflammatory activation of endothelial cells by reactive oxygen species produced during SUA metabolism, thereby triggering a cascade of reactions leading to endothelial damage. This process is considered one of the initial triggers of the coagulation cascade. According to Virchow's triad, this process can ultimately promote the occurrence of VTE.³⁰ Therefore, SUA levels would be an important auxiliary indicator for clinicians to assess the risk of developing lower extremity venous thrombosis.

Limitations

The present study has several limitations. First, the data on hospitalized patients with HF were obtained from a single center. This limitation may have led to a relatively smaller sample size and a lower proportion of female patients. To more comprehensively explore the sex differences in adverse outcomes, the study cohort must be expanded to include a broader patient population. Second, the retrospective design of this study, coupled with the extended duration of data collection and the limited number of samples, restricted our ability to comprehensively assess the laboratory results and dynamic changes in

patients' conditions. Third, recent evidence indicates that the CHA₂DS₂-VASc risk score has independent prognostic value in patients with HF, regardless of the presence of atrial fibrillation (PMID: 23828875 and PMID: 35294768). Incorporating the CHA₂DS₂-VASc score into clinical practice may provide a more comprehensive tool for evaluation and prognostic risk stratification in patients with HF. Fourth, the inability to perform or implement coronary angiography in some patients prevented us from fully excluding the impact of CAD on the study outcomes. Fifth, this study focused solely on the relationship between HFrEF and concurrent anemia and HU without delving into the severity of anemia and UA levels. Lastly, as a retrospective observational study conducted with an HF cohort, this study is likely affected by selection bias. Thus, these limiting factors should be considered when interpreting and applying the study findings.

Conclusion

Our study findings indicate that sex differences significantly impact the clinical presentation and cardiovascular risk factors in patients with HFrEF and concurrent anemia and HU. Specifically, anemia and HU may exert a synergistic effect that would further exacerbate cardiac functional status. In the HFrEF population, the coexistence of anemia and HU is closely associated with higher mortality and cardiovascular events. These findings provide a strong theoretical basis for clinicians to develop diagnostic and risk factor management and prognostic improvement strategies tailored to sex-specific differences in patients with HF. The findings from this study will facilitate the development of targeted interventions, diagnostics, and therapeutic strategies for patients with HFrEF.

Ethical Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities. (License no. YYFY-LL-2024-042). Given the retrospective design, informed consent was waived without affecting patient rights.

Author Contributions

All authors made a significant contribution to the work reported, whether in conception, study design, execution, data acquisition, analysis, interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the target journal; and agree to be accountable for all aspects of the work.

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Disclosure

Zhengjiang Liu and Bixia Yan are co-first authors for this study. The authors declared no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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