



Thyroid Nodules' Effect on Survival and Cardiovascular Risks in HFrEF Patients with Anemia and Hyperuricemia: A Retrospective Study

Journal:	<i>Science Progress</i>
Manuscript ID	SCI-25-1562
Manuscript Type:	Original Research Article
Date Submitted by the Author:	09-Jul-2025
Complete List of Authors:	Liu, ZhengJiang; Youjiang Medical University for Nationalities, Yan, Bixia; Hunan Normal University Affiliated Hengyang City Central Hospital Huang, Ronghua; Youjiang Medical College for Nationalities Zhou, Yi; Youjiang Medical College for Nationalities, Department of Cardiology, Affiliated Hospital of Youjiang Medical University for Nationalities Pan, Xingshou; Youjiang Medical University for Nationalities
Keywords:	Chronic heart failure, Anemia, Serum uric acid, Thyroid nodule, Venous thrombosis
Abstract:	<p>Objective To explore the link between thyroid nodules and the risk, cardiac function, and prognosis in heart failure patients with reduced ejection fraction (HFrEF) who also have anemia and hyperuricemia.</p> <p>Methods 185 HFrEF patients with anemia and hyperuricemia were divided into a thyroid nodule group (94 patients) and a non-thyroid nodule group (91 patients). Logistic and Cox regression analyses assessed the impact of thyroid nodules on cardiovascular events.</p> <p>Results: The thyroid nodule group showed higher body weight ($P<0.01$), lower pulse rate ($P=0.008$), and increased rates of coronary heart disease, hypertension, atrial fibrillation, and diabetes ($P<0.05$ or $P<0.01$). Differences were observed in mean corpuscular volume and prothrombin activity ($P<0.05$). Logistic regression identified coronary heart disease ($OR=2.993$), atrial fibrillation ($OR=2.784$), diabetes ($OR=2.081$), and carotid intima-media thickening with plaques ($OR=2.752$) as significant risk factors. Hypertension negatively impacted cardiac function classification ($OR=0.296$), while mean corpuscular volume ($OR=1.030$) and free thyroxine ($OR=1.101$) increased the risk of cardiac function decline. ROC analysis showed serum uric acid (SUA) better predicted lower extremity venous thrombosis in the non-thyroid nodule group ($AUC=0.809$) than in the thyroid nodule group ($AUC=0.692$). Cox regression indicated thyroid nodules independently predicted mortality ($HR=1.58$, 95% CI: 1.01–2.48, $P=0.048$), whereas atrial fibrillation was linked to reduced mortality risk ($HR=0.523$, $P<0.001$).</p> <p>Conclusion Thyroid nodules are closely associated with multiple cardiovascular risk factors in HFrEF patients with anemia and hyperuricemia and influence patient prognosis, suggesting the need for clinical attention to cardiovascular risk assessment and management in patients with thyroid nodules.</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SCHOLARONE™
Manuscripts

Dear editor

We are pleased to submit our manuscript "Thyroid Nodules' Effect on Survival and Cardiovascular Risks in HFrEF Patients with Anemia and Hyperuricemia: A Retrospective Study" for consideration in Science Progress.

Thyroid nodules independently predicted higher mortality (HR=1.58, *p*=0.046) in HFrEF patients with anemia/hyperuricemia. Serum uric acid better predicted venous thrombosis in non-nodule patients (AUC=0.809 vs. 0.692). FT4 and MCV were associated with cardiac function decline, suggesting new risk markers.

First to link thyroid nodules with cardiovascular outcomes in this high-risk population. Provides actionable insights for integrated thyroid-cardiac risk assessment.

This work aligns with Science Progress focus on cardiovascular/metabolic disorders. We appreciate your consideration and look forward to your response.

This is an original manuscript and has not been previously published or submitted to another journal. There are no conflicts of interest related to the study design or its results.

Sincerely,

Zhengjiang Liu

Department of Cardiology, Affiliated Hospital of Youjiang Medical University for Nationalities,

Youjiang Medical University for Nationalities

j29542006@vip.tom.com

Thyroid Nodules' Effect on Survival and Cardiovascular Risks in HFrEF Patients with Anemia and Hyperuricemia: A Retrospective Study.

Zhengjiang Liu^{*#1}, Bixia Yan^{#2}, Ronghua Huang¹, Yi Zhou¹, Xingshou Pan¹,

¹Department of Cardiology, Affiliated Hospital of Youjiang Medical University for Nationalities, Youjiang Medical University for Nationalities, Baise, Guangxi 533000, P.R. China.
²Affiliated Hengyang Hospital of Hunan Normal University & Hengyang Central Hospital, Hengyang, 421001, Hunan, China

[#]Zhengjiang Liu and Bixia Yan contributed equally to this work and should be considered co-first authors.

*Correspondence to: Dr Zhengjiang Liu, j29542006@vip.tom.com
Department of Cardiology, Affiliated Hospital of Youjiang Medical University for Nationalities, Guangxi Nanning Eighth People's Hospital, Youjiang Medical University for Nationalities, Baise, Guangxi 533000, P.R. China.
Ethical approval: this study was obtained from the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities. (YYFY-LL-2024-042).
Conflicts of interest: The authors declare that they have no competing interests.
Funding: This study was supported by Batch of High-level Talent Scientific Research Projects of the Affiliated Hospital of Youjiang Medical University for Nationalities in 2022. Key Laboratory of Research on Clinical Molecular Diagnosis for High Incidence Diseases in Western Guangxi of Guangxi Higher Education Institutions.

Thyroid Nodules' Effect on Survival and Cardiovascular Risks in HFrEF Patients with Anemia and Hyperuricemia: A Retrospective Study

Abstract

Objective To explore the link between thyroid nodules and the risk, cardiac function, and prognosis in heart failure patients with reduced ejection fraction (HFrEF) who also have anemia and hyperuricemia.

Methods 185 HFrEF patients with anemia and hyperuricemia were divided into a thyroid nodule group (94 patients) and a non-thyroid nodule group (91 patients). Logistic and Cox regression analyses assessed the impact of thyroid nodules on cardiovascular events.

Results: The thyroid nodule group showed higher body weight ($P<0.01$), lower pulse rate ($P=0.008$), and increased rates of coronary heart disease, hypertension, atrial fibrillation, and diabetes ($P<0.05$ or $P<0.01$). Differences were observed in mean corpuscular volume and prothrombin activity ($P<0.05$). Logistic regression identified coronary heart disease (OR=2.993), atrial fibrillation (OR=2.784), diabetes (OR=2.081), and carotid intima-media thickening with plaques (OR=2.752) as significant risk factors. Hypertension negatively impacted cardiac function classification (OR=0.296), while mean corpuscular volume (OR=1.030) and free thyroxine (OR=1.101) increased the risk of cardiac function decline. ROC analysis showed serum uric acid (SUA) better predicted lower extremity venous thrombosis in the non-thyroid nodule group (AUC=0.809) than in the thyroid nodule group (AUC=0.692). Cox regression indicated thyroid nodules independently predicted mortality (HR=1.58, 95% CI: 1.01–2.48, $P=0.048$), whereas atrial fibrillation was linked to reduced mortality risk (HR=0.523, $P<0.001$).

Conclusion Thyroid nodules are closely associated with multiple cardiovascular risk factors in HFrEF patients with anemia and hyperuricemia and influence patient prognosis, suggesting the need for clinical attention to cardiovascular risk assessment and management in patients with thyroid nodules.

Keywords Chronic heart failure, Anemia, Serum uric acid, Thyroid nodule, Thyroid hormone; Venous thrombosis

Introduction

Heart failure (HF) poses a major global health challenge, affecting over 64 million people and ranking as one of the leading causes of morbidity and mortality worldwide. Despite advances in pharmacological and device therapies, the prognosis for HF patients remains poor, with first-year mortality rates ranging from 4% to 45% and an average mortality rate of approximately 33%.¹⁻³ Anemia and hyperuricemia (HUA) are common comorbidities in patients with heart failure with reduced left ventricular ejection fraction (HFrEF), associated with more severe clinical symptoms and adverse outcomes.^{4,5}

Thyroid nodules are a prevalent thyroid disorder, and their detection rate has been increasing annually with the widespread use of ultrasound technology. Existing studies have demonstrated a close relationship between thyroid dysfunction and cardiovascular system function, influencing cardiac structure, function, and vascular endothelial function.⁶ However, as a structural alteration of the thyroid gland, the association between thyroid nodules and cardiovascular diseases remains incompletely understood. Cardiovascular diseases are among the leading causes of death globally, and early identification of cardiovascular risk factors related to thyroid nodules is crucial for improving patient prognosis.

This study aims to explore the correlation between thyroid nodules and the risk of cardiovascular disease occurrence, cardiac function classification, and patient prognosis, providing a theoretical basis for clinical diagnosis and treatment.

Methods

Data source

A retrospective cohort study design was adopted, enrolling hospitalized patients with a primary discharge diagnosis of heart failure from the Department of Cardiovascular Medicine of our hospital between January 1, 2018, and September 1, 2022. A total of 185 patients with HFrEF complicated by anemia and hyperuricemia were included. This study was approved by the Institutional Review Board of our hospital and complied with the Declaration of Helsinki.

Study participants

setting and population Inclusion criteria: (1) Meeting the diagnostic criteria for HFrEF as defined by the European Society of Cardiology [7]; (2) Left ventricular ejection fraction (LVEF) <40% with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels; (3) Age 18 - 85 years. Exclusion criteria: (1) Use of xanthine oxidase inhibitors, urate-lowering drugs, or colchicine; (2) History of thyroid treatment or abnormal thyroid function; (3) Comorbid severe hepatic or renal insufficiency; (4) Comorbid malignancy; (5) Active tuberculosis or other infectious diseases; (6) Severe mental illness; (7) History of major surgical procedures.

Anemia was diagnosed according to WHO criteria: hemoglobin <120 g/L for non-pregnant

women and <130 g/L for men. Hyperuricemia was diagnosed based on the "Multidisciplinary Expert Consensus on Diagnosis and Treatment of Hyperuricemia-Related Diseases in China (2023 Edition)": fasting serum uric acid >420 μ mol/L on two separate occasions. Eligible patients were divided into a thyroid nodule group (91 cases) and a non-thyroid nodule group (94 cases).

Research Methods

Ultrasonography: Philips EPIQ5 and Hitachi Ascendus color Doppler ultrasound diagnostic systems were used. Two experienced sonographers independently analyzed thyroid nodule characteristics (size, orientation, margin, structure, echogenicity, etc.) and cardiac structure/function parameters. Discrepancies were resolved by a third physician.

Laboratory Testing: Venous blood samples were collected from all subjects after an 8-hour fast following hospital admission. Chemiluminescent immunoassay was employed to measure complete blood count, thyroid hormone levels, and biochemical parameters using the Abbott ARCHITECT automated immunoassay analyzer (Abbott Laboratories, USA) with reagents provided by Abbott.

Data collection

Baseline data on demographics, clinical characteristics, laboratory tests, and medication treatments were retrieved from hospital records. The primary composite endpoints included all-cause mortality, heart failure rehospitalization, and cardiovascular events (acute coronary syndrome, stroke). Data were collected through electronic medical record reviews and telephone follow-ups, with the follow-up period ending on January 31, 2024.

Statistical Analysis

Statistical analyses were performed using SPSS (IBM SPSS, Inc., Armonk, New York, USA) and Prism (GraphPad Software, Inc., San Diego, California, USA) software. Continuous measurement data were first subjected to the Shapiro-Wilk test. If they conformed to a normal distribution, they were expressed as mean \pm standard deviation, and intergroup comparisons were conducted using Student's t-test. When comparing demographic characteristics between the two groups, continuous data were analyzed using the Wilcoxon-Mann-Whitney test, while categorical data were presented as percentages and analyzed using the χ^2 test or Fisher's exact test to assess differences. ROC curve analysis was used to evaluate the diagnostic value of SUA for lower extremity venous thrombosis. Kaplan-Meier survival analysis was employed to assess long-term outcomes between the two groups, and the log-rank test was used for intergroup comparisons. To identify cardiovascular risk factors in HFrEF patients with anemia and hyperuricemia (HUA), relevant variables were subjected to univariate analysis ($P \leq 0.1$). Significant variables were then included in multivariate Cox regression analysis to determine independent predictors associated with adverse outcomes, with a two-sided $P < 0.05$ considered statistically significant.

Results

Comparison of Baseline Characteristics Between the Two Groups

A total of 185 patients met the inclusion and exclusion criteria, including 91 (49.2%) in the thyroid nodule group and 94 (50.8%) in the non-thyroid nodule group. Compared to the non-thyroid nodule group, patients in the thyroid nodule group had significantly higher body weight and slower pulse rates at admission ($P < 0.01$). The prevalence of coronary heart disease, hypertension, atrial fibrillation, and diabetes was significantly higher in the thyroid nodule group than in the non-thyroid nodule group, with statistically significant differences ($P < 0.05$ or $P < 0.01$). (See Table 1)

Table 1 Comparison of baseline characteristics between the two groups of patients

For Peer Review

Female	30(16.2)	27(14.6)	0.462	0.497
Male	64(34.6)	64(34.6)		
Age (years)	71.472±7.75	70.29±10.36	6.321	0.253
Weight (Kg)	59.48±10.96	55.13±8.09	9.123	0.000
Pulse Rate (bpm)	85.56±18.25	91.40±20.24	0.038	0.008
Systolic blood pressure (mmHg)	135.32±27.16	129.55±25.65	0.403	0.055
Dystolic blood pressure (mmHg)	80.84±13.38	80.98±17.33	4.829	0.939
Heart Rate (bpm)	90.42±20.79	94.19±23.39	0.579	0.133
Somker	47 (0.01)	44 (49.2)	0.180	0.671
Co-morbidities				
Coronary heart disease	84 (42.47)	133 (21.08)	13.581	0.000
Hypertension	61 (39.35)	94 (24.19)	7.205	0.007
Atrial fibrillation	26 (43.33%)	65 (29.68)	3.994	0.046
Valvular Heart Disease	36 (27.69)	55 (36.91)	2.686	0.101
Cardiomyopathy	48 (35.82)	43 (29.66)	1.205	0.272
Diabetes mellitus	41 (42.27)	50 (27.47)	6.302	0.012
Renal insufficiency	57 (35.41)	34 (28.81)	1.346	0.246
Thrombosis of the deep leg veins	9 (47.37)	82 (31.54)	2.019	0.155
NYHA class				
III	49 (53.8)	53 (56.4)	0.166	0.684
IV	42 (46.2)	41 (43.6)		

Comparison of Laboratory Indicators Between the Two Groups of Patients at Admission

The comparison of routine laboratory and biochemical indicators between the two groups of patients upon admission revealed the following statistically significant differences ($P < 0.05$): The mean corpuscular volume (MCV), prothrombin activity, fibrinogen level, and the ratio of free triiodothyronine (FT3) to free thyroxine (FT4) were higher in the thyroid nodule group compared to the non-thyroid nodule group. In contrast, the mean values of total bilirubin, direct bilirubin, FT4, and aortic valve regurgitation area were lower in the thyroid nodule group ($P < 0.05$ or $P < 0.01$). No significant differences were observed in other laboratory indicators ($P > 0.05$) (see Table 2).

Table 2. Comparison of Relevant Laboratory Indicators in Patients with Thyroid Nodules

Variable	Thyroid nodule group (%)	Non-thyroid nodule group (%)	t/Z	p
MCV(μm^3)	89.49±8.77	86.21±12.35	16.	0.0
Prothrombin activity (%)	73.78 ± 23.59	67.01±21.14	0.0	0.0
Fibrinogen level(g/L)	3.78±1.04	3.41±1.09.	0.0	0.0
Total	10.11±0.82	13.02±1.18	10.	0.0

1							
2							
3	bilirubin(μmol/L)				54	44	
4	Direct	bilirubin	5.01±0.42	6.87±0.67	12.	0.0	
5	(μmol/L)				37	20	
6	FT4(pmol/L)		17.13±3.29	18.44±3.15	0.9	0.0	
7					71	06	
8	Aortic	valve	regurgitation	2.59±0.31	3.95±0.55	6.8	0.0
9	area(cm2)				27	15	
10	FT3/FT4		0.22±0.07	0.19±0.06	1.8	0.0	
11					13	02	
12							
13							
14							

Logistic Regression Analysis of Influencing Factors for Thyroid Nodules in Two Groups of Patients

After gradually incorporating the statistically significant variables into the logistic regression analysis, the results showed that coronary heart disease, atrial fibrillation, diabetes, and bilateral carotid intima-media thickening with plaques significantly increased the risk in the thyroid nodule patient group. This suggests that thyroid nodules may be closely associated with various cardiovascular diseases and risk factors (see Table 3).

Table 3 Logistic Regression Analysis of Influencing Factors for Thyroid Nodules in Two Groups of Patients

Variable	B	SE	Wald	df	p	Exp(B)	95% EXP (B) CI
Atrial fibrillation	1.024	0.394	6.763	1	0.009	2.784	1.278-6.117
Coronary heart disease	1.096	0.318	11.865	1	0.001	2.993	1.142-4.319
Diabetes mellitus	0.733	0.336	4.748	1	0.029	2.081	1.033-3.895
Bilateral carotid intima - media thickening with plaques	1.012	0.500	4.101	1	0.043	2.752	1.033-7.331

Logistic regression analysis of influencing factors on cardiac function classification in the two patient groups

After gradually incorporating the statistically significant variables into the logistic regression analysis, the results showed that hypertension had a significant negative impact on cardiac function classification, with hypertensive patients exhibiting lower cardiac function grades. Both mean corpuscular volume and free thyroxine significantly increased the risk of cardiac function deterioration, indicating that these two factors may play important roles in worsening cardiac function (see Table 4).

Table 4. Logistic regression analysis of influencing factors on cardiac function classification in the two patient groups

Variable	B	SE	Wald	df	p	Exp(B)	95% EXP (B) CI
Hypertension	-1.219	0.272	20.14	1	0.000	0.296	0.174-0.504
MCV(μm^3)	0.029	0.012	6.386	1	0.012	1.030	1.007-1.053

FT4(pmol/L)	0.096	0.041	5.516	1	0.019	1.101	1.016-1.193
-------------	-------	-------	-------	---	-------	-------	-------------

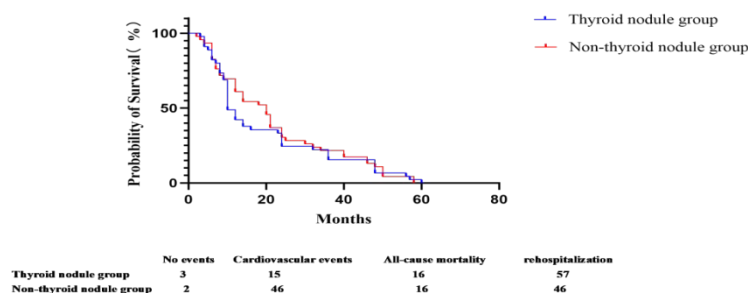
The predictive value of serum uric acid (SUA) for lower extremity venous thrombosis.

ROC curve analysis results from the two groups showed: In terms of the area under the ROC curve, the area under the ROC curve for uric acid in patients with thyroid nodules was 0.692 (95% CI = 0.489 - 0.895), with a sensitivity of 88.9%, specificity of 25.6%, optimal cutoff value of 484 $\mu\text{mol/L}$, and $P = 0.059$. For patients without thyroid nodules, the area under the ROC curve was 0.809 (95% CI = 0.721 - 0.897), with a sensitivity of 80%, specificity of 74.2%, optimal cutoff value of 602.5 $\mu\text{mol/L}$, and $P = 0.045$. Although neither group achieved extremely high diagnostic accuracy, the serum uric acid in patients without thyroid nodules demonstrated better diagnostic value in predicting lower extremity venous thrombosis compared to those with thyroid nodules.

3.6 Cox regression analysis of factors influencing survival time in the two patient groups

During a median follow-up period of 21.78 months (interquartile range: 19.42 - 24.14), a total of 181 patients (99.5%) experienced at least one confirmed adverse outcome. Among these, 118 patients (63.8%) were hospitalized due to progression of heart failure, 24 patients (13%) died, and 38 patients (20.5%) experienced cardiovascular events. The median survival time was 10.0 months (95% CI: 8.0 - 12.0) in the thyroid nodule group and 13.5 months (95% CI: 11.0 - 16.0) in the non-thyroid nodule group, indicating a 3.5-month reduction in survival time for patients with thyroid nodules. The log-rank test confirmed a statistically significant difference ($\chi^2 = 7.906$, $P = 0.048$), demonstrating a notable disparity in survival outcomes between patients with thyroid nodules and those without (Figure 1). This suggests that thyroid nodules are associated with poor prognosis.

Figure 1 Kaplan-Meier survival curve analysis of patients with thyroid nodules



Multivariate Cox regression analysis

The independent prognostic value of comorbidities was evaluated using a stepwise Cox proportional hazards model. After adjusting for atrial fibrillation, thyroid nodules remained a

significant predictor of mortality (HR=1.58, 95% CI: 1.01-2.48, $P=0.046$). Among cardiovascular comorbidities, atrial fibrillation (HR=0.523, 95% CI: 0.426-0.641, $P<0.001$) was associated with a reduced risk of death.

Discussion

This study is the first to systematically investigate the relationship between thyroid nodules and cardiovascular risk and prognosis in patients with HFrEF complicated by anemia and hyperuricemia. The main findings include: (1) Patients with thyroid nodules bear a heavier burden of cardiovascular comorbidities; (2) Thyroid nodules are independently associated with adverse prognosis; (3) SUA demonstrates superior predictive value for lower extremity venous thrombosis in the non-nodule group; (4) Hypertension exhibits a negative correlation with cardiac function classification, while MCV and FT4 increase the risk of cardiac function deterioration.

The results of this study indicate that patients with thyroid nodules tend to have higher body weight and a higher incidence of coronary heart disease, hypertension, atrial fibrillation, and diabetes, suggesting a significantly increased risk of cardiovascular disease in these patients. This may be related to potential subclinical thyroid dysfunction, inflammatory responses, and metabolic disorders associated with thyroid nodules. These factors can promote the occurrence and progression of cardiovascular diseases by affecting food intake, blood, lipid, glucose metabolism, and vascular endothelial function, thereby influencing the prognosis of cardiovascular disease patients.⁸⁻¹⁵

Thyroid dysfunction is associated with an increased risk of venous thrombosis through its effects on von Willebrand factor (VWF) and coagulation factor VIII (FVIII).¹⁶ This study found that SUA has higher predictive value for lower extremity venous thrombosis in the non-thyroid nodule group, possibly because elevated SUA in this group is accompanied by increased free thyroxine (FT4), which regulates serum uric acid concentration by influencing purine nucleotide metabolism and promoting uric acid excretion.¹⁷ This leads to a more significant interaction between coagulation factors (such as FVIII, FIX, FX) and VWF with uric acid metabolism, resulting in an increased risk of lower extremity venous thrombosis.¹⁸⁻²³ This finding has important implications for clinical risk stratification. In clinical practice, cardiovascular risk assessment should be strengthened, and comorbidity management should be optimized for these patients.

Notably, this study found that in patients with HFrEF complicated by anemia and hyperuricemia, blood pressure has a significant negative impact on cardiac function classification, which differs from traditional understanding. This may be related to the overall severity of heart failure in this HFrEF population with anemia and hyperuricemia, the specificity of strict blood pressure control therapy in patients with higher admission blood pressure, and potential confounding factors. This suggests that heart failure involves different underlying pathophysiological mechanisms, requiring further validation through larger sample sizes and multicenter studies.

Within the normal range of thyroid function, higher concentrations of FT4 are associated with an increased risk of atrial fibrillation and heart failure, while lower concentrations of FT4 are

associated with a reduced risk of multiple adverse events, including mortality, in the elderly. A positive correlation exists between T4 levels and increased cardiovascular mortality and morbidity.²⁴⁻³⁰ Elevated MCV indicates morphological changes in red blood cells, resulting in macrocytes that persist longer in circulation without remodeling, exacerbating microcirculatory flow obstruction and leading to impaired extracellular antioxidant capacity, redox imbalance, and altered homeostasis.^{31,32} High MCV reflects numerous underlying conditions (bone marrow dysfunction, malnutrition, organ dysfunction, endothelial dysfunction), and these underlying issues ultimately contribute to adverse prognosis.³³⁻³⁶

In patients with HFrEF complicated by anemia and hyperuricemia, these conditions interact and exacerbate each other, leading to significantly worsened prognosis and reduced survival rates. For these categories of heart failure patients with comorbidities, potential subclinical thyroid dysfunction associated with thyroid nodules involves different underlying pathophysiological mechanisms, and thyroid nodules may influence patient prognosis through multiple pathways. Our findings suggest that atrial fibrillation may have a protective effect on cardiovascular outcomes in patients with thyroid nodules, prolonging survival time. This may be related to long-term anticoagulation therapy (e.g., warfarin, rivaroxaban) or heart rate management medications (e.g., beta-blockers) in atrial fibrillation patients, indirectly reducing the risk of other cardiovascular events (e.g., thrombosis, myocardial ischemia). Whether the complex interaction between thyroid hormones and the heart plays a biphasic role requires further research.

This study has several limitations: First, thyroid nodules and thyroid function were only assessed at admission, without testing for thyroid autoantibodies, and no evaluation of thyroid nodules or thyroid function was conducted during follow-up. Second, this was a single-center, retrospective, observational study with a relatively small sample size, potentially introducing selection bias. Third, the study was cross-sectional and retrospective, making it difficult to establish causality. Finally, some potential influencing factors were not included in the analysis, which may have affected the results. Future multicenter, large-sample, prospective studies are needed to further explore the relationship between thyroid nodules and cardiovascular diseases.

Conclusion

In conclusion, in patients with HFrEF complicated by anemia and hyperuricemia, thyroid nodules are independently associated with a heavier burden of cardiovascular comorbidities and adverse prognosis. Clinicians should prioritize cardiovascular risk assessment in these patients and optimize comprehensive management strategies to improve prognosis.

Acknowledgments

Not applicable

Authors' contributions:

PX carried out the studies and participated in data collection. RH and YZ participated in the design of the study and performed the statistical analysis. ZL and BY conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Data availability statement: Data available upon reasonable request to the corresponding author. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate: Data available upon reasonable request to the corresponding author. Due to the retrospective nature of the study, it did not affect participants' rights. Therefore, all subjects were exempted from providing informed consent. All medical data were fully protected, with personal data deleted and coded as arbitrary numbers.

Funding: This study was supported by Batch of High-level Talent Scientific Research Projects of the Affiliated Hospital of Youjiang Medical University for Nationalities in 2022. Key Laboratory of Research on Clinical Molecular Diagnosis for High Incidence Diseases in Western Guangxi of Guangxi Higher Education Institutions.

References

1. Savarese, G, Becher PM, Lund LH, et al, Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res.* 2023 Jan 18; 118(17): 3272-3287.

2. Emmons-Bell S, Johnson C, Roth G. Prevalence, incidence and survival of heart failure: a systematic review. *Heart.* 2022 Aug 11 ; 108(17): 1351-1360.

3. Wintrich J, Berger AK, Bewarder Y, et al. Neues zur Diagnostik und Therapie der Herzinsuffizienz[Update on diagnostics and treatment of heart failure]. *Herz.* 2022 Aug; 47(4): 340-353.

4. Stubnova V, Os I, Høieggen A, et al. Gender differences in association between uric acid and all-cause mortality in patients with chronic heart failure. *BMC Cardiovasc Disord.* 2019 Jan 5; 19(1): 4.

5. Fu K, Cheng C, Su C, et al. Gender differences in the relationship between serum uric acid and the long-term prognosis in heart failure: a nationwide study. *Cardiovasc Diabetol.* 2024 Apr 18; 23(1): 131.

6. Dabravolski SA, Churov AV, Elizova NV, et al. Association between atherosclerosis and the development of multi-organ pathologies. *SAGE open medicine.* 2024 Dec 23; 12: 20503121241310013.

7. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021 Jan 27; 42(36): 3599–3726.

8. Corona G, Croce L, Sparano C, et al. Thyroid and heart, a clinically relevant relationship. *J Endocrinol Invest.* 2021 Dec; 44(12): 2535-2544.

9. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid.*

2016 Oct 26; 26(10): 1343-1421.

10. Davis PJ, Goglia F, Leonard JL. Nongenomic actions of thyroid hormone. *Nat Rev Endocrinol*. 2016 Feb; 12: 111–121.

11. Casis O, Echeazarra L, Sáenz-Díez B, et al. Deciphering the roles of triiodothyronine (T3) and thyroid-stimulating hormone (TSH) on cardiac electrical remodelling in clinical and experimental hypothyroidism. *J Physiol Biochem*. 2024 Feb; 80: 1–9.

12. Wang W, Wang S, Zhang K, et al. Hypothyroidism is associated with clinical outcomes in patients with acute myocardial infarction: subgroup analysis of China PEACE study. *Endocrine*. 2021 Jun ; 74(1):128-137.

13. Ramouzi E, Sveroni K, Manou M, et al. The Impact of Thyroid Hormones on Cardiometabolic Risk in Children and Adolescents with Obesity, Overweight and Normal Body Mass Index (BMI): A One-Year Intervention Study. *Nutrients*. 2024 Aug 11; 16(16): 2650.

14. Cooper DS, Biondi B. Subclinical hypothyroidism. *Lancet*. 2012; 379(9821): 1142-1154.

15. Tian H, Xie C, Teng B, et al. The genetic effects of hormones modulated by the Pituitary-Thyroid/Adrenal/Gonadal axis on the risk of developing venous thromboembolism: a mendelian randomization study. *BMC Cardiovasc Disord*. 2024 Jul 25; 24(1):v383.

16. Xie H, Li N, Zhou G, et al. The association between the thyroid feedback quantile-based index and serum uric acid in U.S. adults. *Eur. J. Med. Res*. 2023 Jul 27 ; 28: 259.

17. Stuijver DJ, van Zaane B, Romualdi E, et al. The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors: a systematic review and meta-analysis. *Thromb Haemost*. 2012 Dec;108(6):1077-1088.

18. Squizzato A, Van Zaane B, Gerdes VE, et al. The influence of Pituitary, adrenal, and parathyroid hormones on hemostasis and thrombosis. *Semin Thromb Hemost*. 2011 Feb; 37(1):41–48.

19. Elbers LP, Moran C, Gerdes VE, et al. The hypercoagulable state in hyperthyroidism is mediated via the thyroid hormone β receptor pathway. *Eur J Endocrinol*. 2016 Mar 9; 174(6):755–762.

20. Stuijver DJ, van Zaane B, Feelders RA, et al. Incidence of venous thromboembolism in patients with Cushing's syndrome: a Multicenter Cohort Study. *J Clin Endocrinol Metabolism*. 2011 Nov; 96(11): 3525–3532.

21. Wagner J, Langlois F, Lim DST, et al. Hypercoagulability and Risk of Venous Thromboembolic Events in Endogenous Cushing's Syndrome: A Systematic Meta-Analysis. *Front Endocrinol*. 2019 Jan 28; 9: 805.

22. Debeij J, van Zaane B, Dekkers OM, et al. High levels of procoagulant factors mediate the association between free thyroxine and the risk of venous thrombosis: the MEGA study. *J Thromb Haemost*. 2014 Jun; 12(6): 839–846.

23. Cappola AR, Arnold AM, Wulczyn K, et al. Thyroid function in the euthyroid range and adverse outcomes in older adults. *J Clin Endocrinol Metab*. 2015 Mar; 100(3): 1088-1096.

24. Einfeldt MN, Olsen A-MS, Kristensen SL, et al. Long-term outcome in patients with heart failure treated with levothyroxine: an observational nationwide cohort study. *J Clin Endocrinol Metab*. 2019 May 1; 104: 1725–1734.

25. Eagan D, Spencer-Bonilla G, Maraka S, et al. Management of hypothyroidism in patients with acute myocardial infarction. *Med (Kaunas)*. 2020 Apr 28; 56: 214.

26. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for

Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016 Oct; 26(10):1343-1421.

27. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation*. 2014 Jan 21; 129(3): e28-e292.

28. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001 Feb 15; 344(7): 501-509.

29. Xu Y, Derakhshan A, Hysaj O, et al. The optimal healthy ranges of thyroid function defined by the risk of cardiovascular disease and mortality: systematic review and individual participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2023 Oct; 11(10): 743-754.

30. Kaferle J, Strzoda CE. Evaluation of macrocytosis. *Am Fam Physician*. 2009 Feb 1; 79(3): 203–208.

31. Tsantes AE, Bonovas S, Travlou A, et al. Redox imbalance, macrocytosis, and RBC homeostasis. *Antioxid Redox Signal*. 2006 Jul-Aug; 8(7–8): 1205–1216.

32. Norton JM. The effect of macrocytosis on rat erythrocyte deformability during recovery from phenylhydrazine-induced anemia. *Biorheology*. 1990 Jan 1; 27(1): 21–37.

33. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. *Clin Med Res*. 2006 Dec; 4(3): 236–241.

34. Oosterhuis WP, Niessen RW, Bossuyt PM, et al. Diagnostic value of the mean corpuscular volume in the detection of vitamin B12 deficiency. *Scand J Clin Lab Invest*. 2000 Jul 8; 60(1): 9–18.

35. Stam F, van Guldener C, Becker A, et al. Endothelial dysfunction contributes to renal function-associated cardiovascular mortality in a population with mild renal insufficiency: the Hoorn study. *J Am Soc Nephrol*. 2006 Feb 31; 17(2): 537–545.

36. Mahmoud MY, Lugon M, Anderson CC. Unexplained macrocytosis in elderly patients. *Age Ageing*. 1996 Jul 1; 25(4): 310–312.