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ORIGINAL RESEARCH

Subclinical Hypothyroidism Predicted Adverse Cardiovascular Events in Patients with Ejection Fraction Preserved Heart Failure

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Background: Subclinical hypothyroidism (SH) increases the risk of cardiovascular events, however the influence of SH on prognosis of ejection fraction preserved heart failure (HFpEF) is not fully understood.

Methods: In this prospective observational study, patients with HFpEF were divided into euthyroidism group (n = 413) and SH group (n = 79). Patients were followed up for at least 30 months to examine the association between SH and cardiovascular events in patients with HFpEF. The primary end point was composite cardiovascular events (cardiovascular death and re-hospitalization). The patients underwent flow-mediated dilation (FMD) measurement by ultrasound in order to value endothelial function.

Results: The rate of composite cardiovascular events was higher in SH group than in euthyroidism group (54.49% and 26.36%, respectively; $p < 0.001$). The higher risk of cardiovascular events in SH group was primarily due to a higher risk of re-hospitalization compared to euthyroidism group (45.56% and 20.58%, respectively; $p < 0.001$). The rate of cardiovascular death was higher in SH group than in euthyroidism group (13.92% and 5.81%, respectively; $p = 0.017$). Cox proportional hazards regression showed that SH (hazard ratios [HR] 1.921, 95% confidence interval [CI] 1.139–3.240), level of TSH (HR 1.025, 95% CI 1.010–1.054), age (HR 1.017, 95% CI 1.002–1.034), LVEF (HR 0.975, 95% CI 0.953–0.996), atrial fibrillation (HR 1.581, 95% CI 1.083–2.307), eGFR (HR 0.987, 95% CI 0.978–0.997), and NYHA cardiac function (HR 2.342, 95% CI 1.649–3.326) were independent predictors of cardiovascular events in patients with HFpEF (all $P < 0.05$).

Conclusion: Subclinical hypothyroidism was associated with increased cardiovascular events and death in patients with HFpEF.

Keywords: subclinical hypothyroidism, ejection fraction preserved heart failure, endothelial function, flow-mediated dilation, cardiovascular events

Introduction

Thyroid hormone participates in several cardiovascular functions, including endothelial function, conduction system, and cardiac construction.[1] Insufficient thyroid hormone leads to ventricular arrhythmias and endothelial dysfunction.[2] Subclinical hypothyroidism is defined as elevated thyroid-stimulating hormone (TSH) levels with normal free thyroid hormone concentrations.[3] Previous studies indicated that subclinical hypothyroidism increases the risk of cardiovascular events.[4,5]

Heart failure (HF) is still a main cause of morbidity and mortality all over the world. According to the left ventricular ejection fraction (LVEF), HF could be classified into HF with reduced ejection fraction (HFrEF), HF with improved ejection fraction (HFimpEF), HF with mildly reduced ejection fraction (HFmEF), and HF with preserved ejection fraction (HFpEF).[6] HFpEF is the most common type of HF in the population. As previous research suggested,[7] subclinical hypothyroidism is associated with poor prognosis of cardiovascular disease, but previous studies have not mentioned whether subclinical hypothyroidism influences prognosis in patients with

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heart failure. To our knowledge, there is no research to explore the association between subclinical hypothyroidism and HFpEF.

The purpose of this study is to investigate whether subclinical hypothyroidism is associated with adverse prognosis in patients with HFpEF.

Methods

Study Population

This was a prospective observational study of patients with HFpEF who were discharged from Qinhuangdao First Hospital between September 2016 and March 2020. The diagnosis of HFpEF was made by two cardiologists on the basis of the HFpEF guidelines.[8] The inclusion criteria are as follows: (1) patients with a diagnosis of HFpEF, the criterion of HFpEF is according to ACC/AHA guidelines (LVEF ≥ 50%, evidence of spontaneous or provokable increased LV filling pressure, NT-pro BNP ≥ 220 pg/mL); (2) New York Heart Association (NYHA) class II–IV; (3) patients aged 25–85 years; and (4) signed informed consent. Exclusion criteria were: (1) patients with acute myocardial infarction; (2) patients receiving amiodarone therapies; (3) patients with thyroxine substitution therapy; (4) patients with carcinoma; (5) patients who did not have thyroid function testing; (6) patients with overt hyperthyroidism, overt hypothyroidism, low-T3 syndrome, and subclinical hyperthyroidism; and (7) patients who received thyroid surgery or antithyroid drugs.

A total of 753 patients were evaluated for inclusion, 514 were enrolled, and 492 completed the follow-up. This study complies with the Declaration of Helsinki. This study was approved by the Ethics Committee of Qinhuangdao First Hospital, and all patients provided written informed consent.

Thyroid Hormone Measurement and Definition of Subgroup

Thyroid hormones (TSH, FT3, and FT4) were measured using electrochemiluminescence immunoassay (Roche Diagnostics, Japan). The normal reference intervals of thyroid hormones in our hospital are: free T3, 1.58 to 3.91 pg/mL; free T4, 0.7 to 1.48 pg/dL; and TSH, 0.45 to 4.49 mIU/L. Patients were divided to the following groups according to serum FT4 and TSH levels. The definition of subclinical thyroid dysfunction is based on expert reviews.[9] Euthyroidism defined as TSH of 0.45 to 4.49 mIU/L with normal FT3 and FT4; subclinical hypothyroidism defined as TSH > 4.49 mIU/L with normal FT4; subclinical hyperthyroidism defined as TSH < 0.45 mIU/L with normal free T4; overt hypothyroidism defined as TSH > 4.49 mIU/L with decreased FT4; and overt hyperthyroidism defined as TSH < 0.45 mIU/L with elevated FT4. Additionally low-T3 syndrome was defined as TSH of 0.45 to 4.49 mIU/L with decreased FT3 (FT3 < 1.58 pg/mL).

FMD Measurement

Flow-mediated dilation (FMD) in the brachial artery is a reliable and noninvasive method of endothelial function assessment. In this study, all enrolled patients underwent flow-mediated dilation (FMD) measurement by ultrasound (VIVID 8 ultrasound system, GE Company). The protocol was followed the methods we established previously.[10,11] FMD was expressed as the percent change of brachial artery diameter ([maximum diameter − baseline diameter] / baseline diameter) × 100%).[10,11]

Follow-Up

Patients were followed up every 6 months for at least 30 months. At each visit, physical examination, 12-lead electrocardiogram and a list of ongoing medications were obtained.[11] Echocardiography was performed at baseline and 24-month follow-up. Transthoracic echocardiography (Vivid 8, GE, Wuxi, China) was performed to evaluate the left atrial diameter (LAD), left ventricular diameter (LVD), and left ventricular ejection fraction (LVEF).[11] All procedures and analyses were performed by an experienced researcher who was blinded to the thyroid hormone results.

Study End Points

The primary end point was a composite of major adverse cardiovascular events (MACE), which included cardiac death and heart failure hospitalization. The second end point was cardiac death. All events were validated by a review of medical records by senior cardiologists.

Statistical Analysis

The statistical analyses were performed using SPSS 19 (version 17; IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation. The Shapiro–Wilk test was used to test for normality of distribution. Categorical variables were compared using the χ^2 statistics or Fisher's exact test. Continuous variables were compared using unpaired Student's *t*-test or Kruskal–Wallis *H*-test. MACE-free survival analyses were performed using the Kaplan–Meier method. The log rank test was used to compare the groups. Cox proportional hazards regression analysis was conducted to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the composite cardiovascular events. Variables with $p < 0.10$ in the univariate analysis were included in the multivariate analysis. $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 753 patients with HFpEF were evaluated for this study. Fifty-eight patients who did not have thyroid function testing were excluded. Moreover, 31 patients receiving thyroxine substitution therapy and 43 patients who receiving amiodarone therapies were excluded. Additionally, 12 patients with carcinoma and 25 patients with acute myocardial infarction were excluded. Eight patients with subclinical hyperthyroidism, 12 patients with overt hypothyroidism, 7 patients with overt hyperthyroidism, and 43 patients with low-T3 syndrome were excluded. The study included 514 patients, of whom 22 were lost during follow-up. Therefore, the final study participants included 492 patients (365 men, 74.2% and 127 women, 25.8%) with a mean age of 66.3 ± 12.1 years (range = 31–85).

Patients were divided into euthyroidism group and the subclinical hypothyroidism group according to values of TSH and free T4. As Table 1 presents, there were no differences in age, gender, etiology of heart failure, cardiac function classification by NYHA, left atrial diameter, and smoking. However, the incidences of diabetes, hypertension, and atrial fibrillation were higher in the subclinical hypothyroidism group than in the euthyroidism group. The left ventricular

Table 1 Clinical Characteristics of Euthyroidism Group and Subclinical Hypothyroidism Group

	Euthyroidism (n = 413)	Subclinical Hypothyroidism (n = 79)	p value
Age	68.08 ± 11.71	69.29 ± 12.92	0.412
Gender (M/F)	238/174	49/30	0.709
Etiology of heart failure			
Ischemic heart disease	239/413	45/79	0.881
Dilated cardiomyopathy	76/413	11/79	0.339
Hypertensive heart disease	29/97	4/79	0.524
Valvular heart disease	51/413	12/79	0.489
Others	24/413	7/79	0.307
Smoking	121/413	19/79	0.344
Diabetes	95/413	28/79	0.023
Hypertension	230/413	55/79	0.022
Atrial fibrillation	159/413	40/79	0.044
LVD (mm)	53.55 ± 9.63	56.16 ± 9.41	0.028
LAD (mm)	45.20± 8.88	46.05 ± 8.61	0.438

(*Continued*)

Table 1 (Continued).

	Euthyroidism (n = 413)	Subclinical Hypothyroidism (n = 79)	p value
LVEF (%)	60.51 ± 8.96	56.71 ± 8.61	0
Mitral valve E/e'	20.86± 11.92	22.76 ± 11.28	0.546
SBP (mmHg)	132.27 ± 24.48	126.54 ± 21.99	0.062
DBP (mmHg)	79.61 ± 16.75	78.71 ± 15.41	0.668
Heart rate (beats/min)	83.23 ± 21.48	84.11 ± 19.85	0.75
NYHA classification			0.088
Class 2	47	3	
Class 3	159	26	
Class 4	207	50	
NT-pro BNP M (IQR)	1251 (382–2894)	3146 (714–6768)	0.001
TSH (mIU/L)	2.21 ±1.83	6.93 ± 4.61	0
FT3 (pg/mL)	1.75 ±1.61	1.86 ±1.06	0.463
FT4 (pg/mL)	1.67 ±0.81	1.87 ±1.07	0.192
TC (mmol/L)	4.06 ±1.25	3.66 ±1.32	0.015
TG (mmol/L)	1.49 ±1.48	1.22 ±0.82	0.015
Glucose (mmol/L)	6.03 ±2.48	6.10 ±2.68	0.822
Creatinine (μmol/L)	92.57 ±72.73	110.50 ±82.96	0.004
eGFR (mL/min/1.73 m^2)	59.841 ±17.99	49.361 ±20.27	0
Uric acid (mmol/L)	415.01 ±158.48	446.92 ±176.83	0.155
Homocysteine (mmol/L)	14.45 ±10.22	19.14 ±11.93	0.001
Serum potassium (mmol/L)	4.01 ±0.51	4.11 ±0.58	0.124
Serum sodium (mmol/L)	143.63 ±14.12	139.26 ±4.38	0.61
BMI (kg/m^2)	24.82 ±4.12	24.99 ±5.01	0.768
FMD (%)	7.42 ±2.01	5.72 ±1.69	0
Diuretic user	279/413	45/79	0.069
Beta blocker user	392/413	72/79	0.184
ACEI/ARB user	234/413	41/79	0.435
ARNI user	134/413	22/79	0.421
Aldosterone inhibitor	301/413	56/79	0.716
SGLT2 inhibitor	123/413	28/79	0.318
Statin user	211/413	48/79	0.09
Aspirin	273/413	45/34	0.12
NOAC	101/413	24/79	0.07
Calcium antagonist	78/413	17/79	0.587
Duration of HF M(IQR)	6 (1–20)	15 (2–36)	0.001

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; LVD, left ventricular diameter; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; FMD, flow-mediated dilatation; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; mitral valve E/e', ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; SGLT2, sodium-dependent glucose transporters 2; eGFR, estimated glomerular filtration rate; ARNI, angiotensin receptor enkephalinase inhibitor; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid stimulating hormone; NOAC, new oral anticoagulants.

diameter was larger, EF was lower, and eGFR score was lower in patients of the subclinical hypothyroidism group compared with the euthyroidism group. Patients in the subclinical hypothyroidism group had higher levels of TSH and NT-pro BNP than patients in the euthyroidism group, but there were no significant difference of FT3 and FT4 between the two groups.

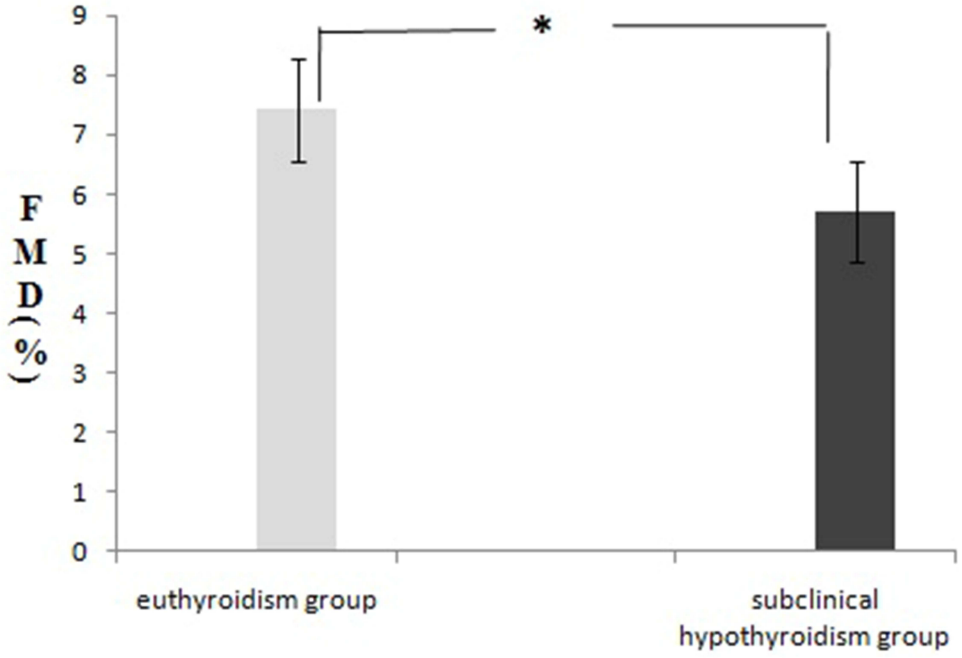

Figure 1 Comparison of FMD between euthyroidism group and subclinical hypothyroidism group. Values of FMD were lower in the subclinical hypothyroidism group compared with the euthyroidism group (*$P < 0.05$).
Abbreviation: FMD, flow-mediated dilation.

FMD Measurement

As shown in Figure 1, the values of FMD were lower in the subclinical hypothyroidism group (5.72 ±1.69%) compared with the euthyroidism group (7.42 ±2.01%) ($P < 0.05$).

Follow-Up and Clinical Outcomes

During a mean follow-up of 33 ± 2.7 months, 156 of the 492 patients had cardiovascular events (primary end point) (Table 2). The rate of composite cardiovascular events was higher in patients in the subclinical hypothyroidism group compared to those in the euthyroidism group (54.49% and 26.36%, respectively; log rank test, $p < 0.001$, Figure 2). The higher risk of cardiovascular events in patients with subclinical hypothyroidism was primarily due to a higher risk of re-hospitalization in these patients compared to those with euthyroidism (45.56% and 20.58%, respectively; log rank test, $p < 0.001$, Figure 3). Moreover, the rate of cardiovascular death was higher in the subclinical hypothyroidism group than in the euthyroidism group (13.92% and 5.81%, respectively; log rank test, $p = 0.017$, Figure 4).

The baseline characteristics of the patients stratified by the primary end point are summarized in Table 3. Compared with the -MACE group, patients with MACE had higher levels of TSH and NT-pro BNP. Patients with MACE also

Table 2 Clinical Outcomes of Euthyroidism and Subclinical Hypothyroidism

	Euthyroidism (n=413)	Subclinical Hypothyroidism (n=79)	p value
Composite cardiovascular events	109 (26.39%)	47 (54.49%)	0.000
Cardiovascular death	24 (5.81%)	11 (13.92%)	0.017
Re-hospitalization	85 (20.58%)	36 (45.56%)	0.000

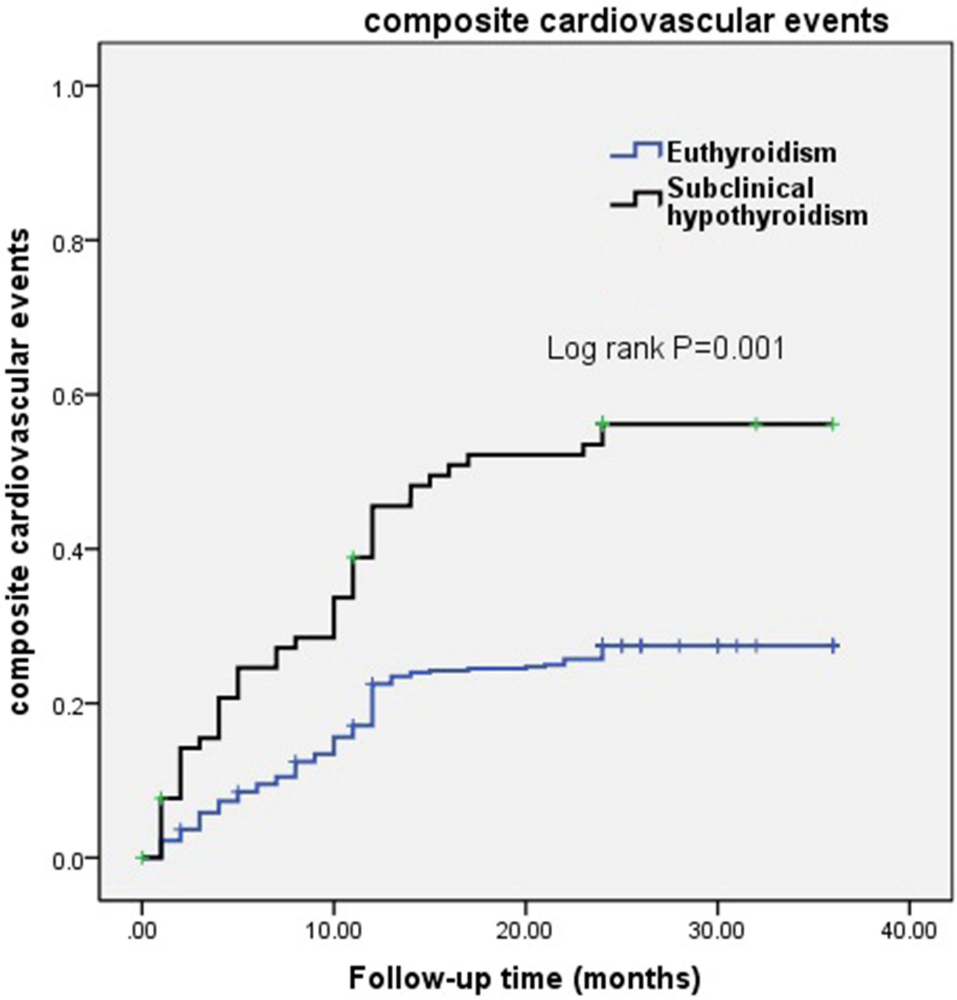

Figure 2 Kaplan–Meier survival curves for composite cardiovascular events for patients with euthyroidism and subclinical hypothyroidism.

showed higher rates of diabetes and atrial fibrillation. The MACE group also had lower LVEF, bigger LVD and LAD, and lower FMD than the non-MACE group.

As Table 4 shows, the results of Cox regression revealed that age (HR 1.017, 95% CI 1.002–1.034), subclinical hypothyroidism (HR 1.921, 95% CI 1.139–3.240), level of TSH (HR 1.025, 95% CI 1.010–1.054), LVEF (HR 0.975, 95% CI 0.953–0.996), AF (HR 1.581, 95% CI 1.083–2.307), eGFR (HR 0.987, 95% CI 0.978–0.997), FMD (HR 0.891, 95% CI 0.804–0.987), and cardiac function classification by NYHA (HR 2.342, 95% CI 1.649–3.326) were independent predictors of cardiovascular events in patients with HFpEF (all $P < 0.05$).

Discussion

The present study demonstrates that subclinical hypothyroidism was associated with increased cardiovascular events and death in patients with HFpEF. The incidence of subclinical hypothyroidism and the elevation of TSH were both predictors of adverse events in these patients.

Patients with subclinical hypothyroidism have normal levels of FT4 and elevated TSH levels. Some previous studies have demonstrated that subclinical hypothyroidism was associated with increased risk of ischemic heart disease and increased cardiovascular mortality.[12,13] There were also studies that illustrated that subclinical hypothyroidism increased cardiac death in patients with pre-existing heart failure. The Penn Heart Failure Study found that thyroid dysfunction with TSH ≥ 7mIU/L and isolated low T3 levels were connected with poor outcomes in patients with HF.[13] Hayashi et al's study also found that subclinical hypothyroidism on

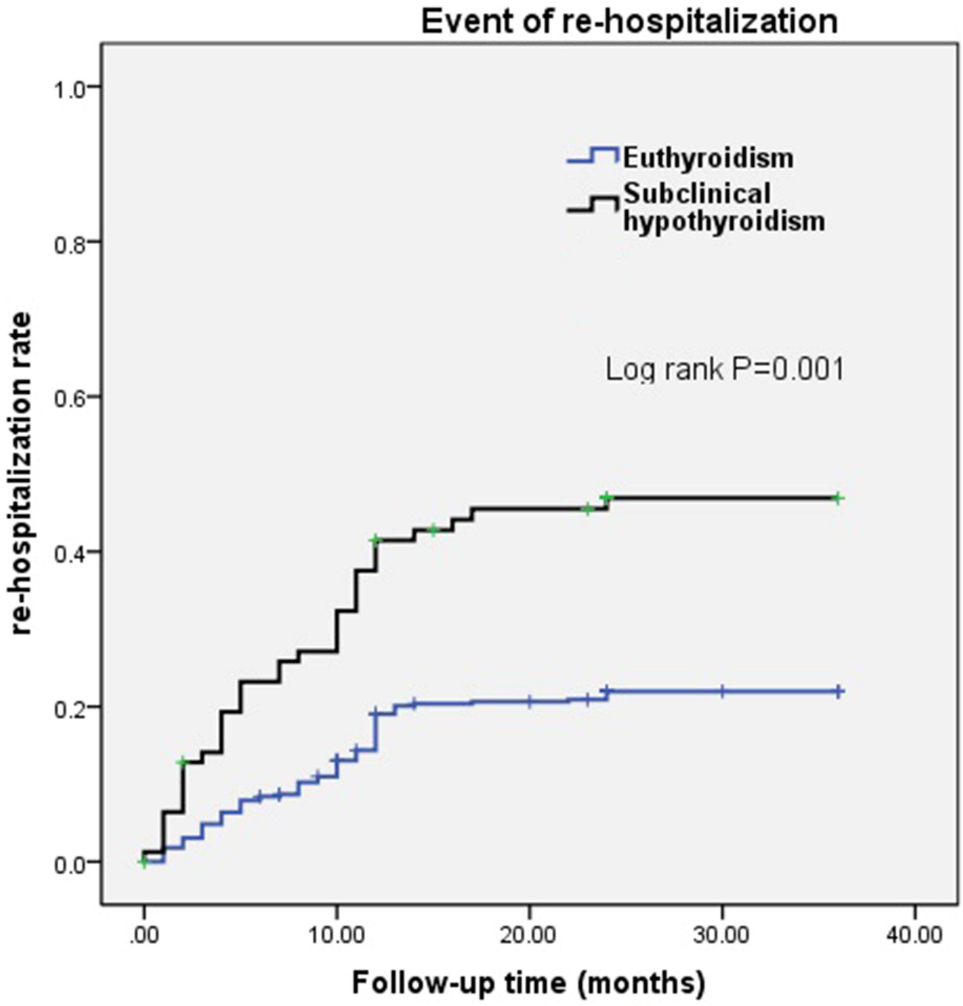

Figure 3 Kaplan–Meier survival curves for re-hospitalization events with euthyroidism and subclinical hypothyroidism.

admission was an independent predictor of adverse cardiovascular outcomes in patients with acute decompensated heart failure.[14] To the best of author knowledge, this is the first report to explore the relationship between subclinical hypothyroidism and HFpEF. We found that the subclinical hypothyroidism group had a worse prognosis than the euthyroidism group in patients with preexisting HFpEF. Subclinical hypothyroidism and the elevation level of TSH were both independent predictors of adverse cardiovascular events. The mechanisms of subclinical hypothyroidism-induced poor prognosis in patients with HFpEF are still unknown. But elevated TSH may play an important role in it. Elevation of TSH could bind to TSH receptor which is expressed on endothelial cells and exert its function. A previous study demonstrated that elevated TSH reduced eNOS and PGI2 expression in human umbilical vein endothelial cells.[15] Dardano et al found that administration of recombinant human TSH could induce inflammation, oxidative stress, and finally impaired endothelial function which was evaluated by FMD.[16]

As a traditional indicator of endothelial function, FMD was decreased in patients with subclinical hypothyroidism in this current study. Also, a declined level of FMD was one of the independent predictors of MACE in this study. These results indicate that subclinical hypothyroidism was associated with endothelial dysfunction. Previous studies demonstrated that endothelial dysfunction plays a significant role in onset and development of cardiovascular diseases.[17,18] Impaired endothelial function may be another possible mechanism by which subclinical hypothyroidism increased cardiac events in patients with HFpEF.

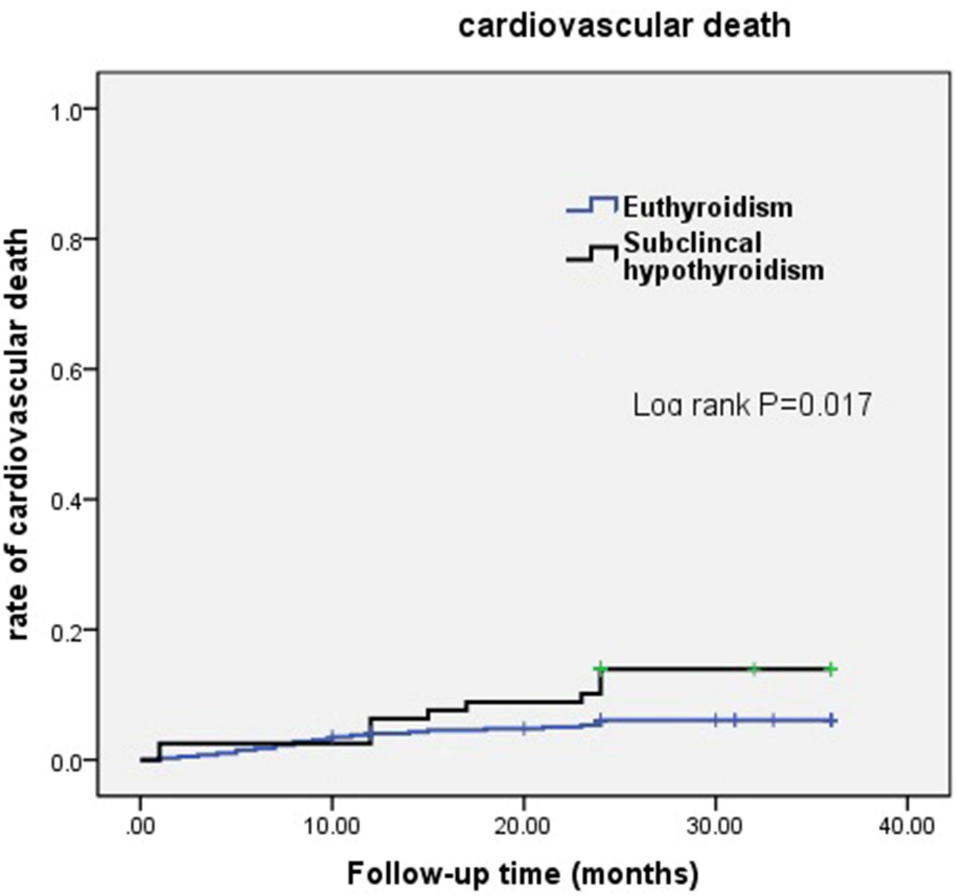

Figure 4 Kaplan–Meier survival curves for cardiovascular death for patients with euthyroidism and subclinical hypothyroidism.

Study Limitations

First, we compared subclinical hypothyroidism and euthyroidism in patients with HFpEF, but we did not enroll patients with clinical hypothyroidism. Further studies are needed to explore the relationship between impaired endothelial function and cardiovascular events in these patients.

Table 3 Clinical Characteristics of Patients with MACE or Without MACE

	MACE Group (n = 157)	Non-MACE Group (n =335)	p value
Age	71.63±12.05	66.72 ± 11.53	0.000
Gender (M/F)	97/60	189/146	0.377
Etiology of heart failure			
Ischemic heart disease	95/157	189/335	0.881
Dilated cardiomyopathy	31/157	56/335	0.339
Hypertensive heart disease	11/157	22/335	0.524
Valvular heart disease	22/157	41/335	0.489
Others	13/157	18/335	0.307
Smoking	47/157	93/335	0.344
Diabetes	53/157	69/335	0.002

(*Continued*)

Table 3 (Continued).

	MACE Group (n = 157)	Non-MACE Group (n =335)	p value
Hypertension	100/157	151/184	0.137
Atrial fibrillation	89/157	109/335	0.000
LVD (mm)	56.72 ± 10.46	52.64 ± 8.95	0.000
LAD (mm)	47.47± 10.08	44.34 ± 8.02	0.001
LVEF (%)	57.02 ± 8.51	61.26 ± 8.82	0.000
Mitral valve E/e'	23.87 ± 13.34	19.06 ± 9.42	0.047
SBP (mmHg)	126.89 ± 29.88	133.59 ± 20.62	0.008
DBP (mmHg)	76.66 ± 18.81	81.03 ± 14.87	0.011
Heart rate (/min)	83.86 ± 23.268	83.21 ± 19.91	0.778
NYHA classification			0.000
Class 2	8	42	
Class 3	32	154	
Class 4	117	139	
BNP M (IQR)	2670 (1035–8575)	920 (296–2520)	0.001
TSH (mIU/L)	3.46 ±3.15	2.73± 1.85	0.004
FT3 (pg/mL)	1.67±1.14	1.82 ±1.67	0.028
FT4 (pg/mL)	1.76 ±0.84	1.87 ±1.01	0.118
TC (mmol/L)	4.06 ±1.25	3.66 ±1.32	0.000
TG (mmol/L)	3.72 ±1.34	4.11 ±1.23	0.000
Glucose (mmol/L)	6.31 ±2.72	5.91 ±2.41	0.001
Creatinine (μmol/L)	122.72 ±105.41	84.67 ±51.57	0.001
eGFR (mL/min/1.73 m^2)	50.49 ±20.80	61.79 ±16.45	0.000
Uric acid (mmol/L)	465.39 ±206.20	397.36 ±127.94	0.246
HCY (mmol/L)	16.61 ±9.59	14.72 ±10.93	0.043
Serum potassium (mmol/L)	4.17 ±0.58	3.93 ±0.48	0.000
Serum sodium (mmol/L)	138.84 ±5.06	144.89 ±8.27	0.397
BMI (kg/m^2)	24.17 ±4.98	25.24 ±3.86	0.021
FMD (%)	6.67 ±1.94	7.38 ±2.08	0.000
Diuretic user	106/157	218/335	0.471
Beta blocker user	145/157	318/335	0.259
ACEI/ARB user	82/157	193/335	0.329
ARNI	53/157	103/335	0.503
Aldosterone inhibitor	123/157	234/335	0.063
SGLT2 inhibitor	47/157	104/335	0.804
Statin user	83/157	176/335	0.945
Aspirin	101/157	217/335	0.923
NOAC	51/157	84/335	0.086
Calcium antagonist	36/157	59/335	0.164
Duration of HF M(IQR)	12 (3–36)	4 (1–12)	0.001

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; LVD, left ventricular diameter; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; FMD, flow-mediated dilatation; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; mvalve E/e', ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; SGLT2, sodium-dependent glucose transporters 2; eGFR, estimated glomerular filtration rate; ARNI, angiotensin receptor enkephalinase inhibitor; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid stimulating hormone; HCY, homocysteine; NOAC, new oral anticoagulants.

Second, comorbidities are highly prevalent in patients with HF and affect outcomes of these patients, but we did not include clinical scores to evaluate comorbidities. The Charlson Comorbidity Index (CCI) or CHA2DS2-Vasc Score were potential predictors of MACE in patients with HF.[19,20] We need further study to explore these predictors.

Table 4 Cox Proportional Hazards Regression Model of Cardiovascular Events in Patients with HFpEF

	Univariate Analysis Coefficient (95% CI)	p value	Multiple Analysis Coefficient (95% CI)	p value
Age	1.031 (1.016—1.046)	0.000	1.017 (1.002–1.034)	0.043
Duration of HF	1.003 (1.001–1.005)	0.001	1.001 (0.998–1.004)	0.383
SH	2.534 (1.782–3.605)	0.000	1.921 (1.139–3.240)	0.014
TSH	1.051 (1.012–1.092)	0.009	1.025 (1.010–1.054)	0.029
LVD	1.031 (1.017–1.045)	0.000	1.012 (0.994–1.031)	0.196
LAD	1.029 (1.014–1.044)	0.000	1.015 (0.994–1.035)	0.157
LVEF	0.964 (0.950–0.978)	0.000	0.975 (0.953–0.996)	0.023
Diabetes	1.676 (1.202–2.336)	0.002	1.029 (0.696—1.521)	0.886
Hypertension	1.356 (0.977–1.882)	0.069	–	–
AF	2.196 (1.579–3.020)	0.004	1.581 (1.083–2.307)	0.018
FMD	0.867 (0.800–0.940)	0.000	0.891 (0.804–0.987)	0.027
eGFR	0.976 (0.968–0.983)	0.000	0.987 (0.978–0.997)	0.008
Homocysteine	1.014 (0.997–1.032)	0.109	–	–
Urine acid	1.002 (1.001–1.003)	0.000	1.011 (1.010–1.012)	0.218
BMI	0.944 (0.903–0.987)	0.011	0.958 (0.915–1.003)	0.069
Serum potassium	1.799(1.362–2.378)	0.000	1.042(0.756–1.438)	0.801
NYHA classification	2.431(1.800–3.283)	0.000	2.342(1.649–3.326)	0.000

Abbreviations: HFpEF, heart failure with preserved ejection fraction; SH, subclinical hypothyroidism; TSH, thyroid stimulating hormone; LVD, left ventricular diameter; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; FMD, flow-mediated dilatation; eGFR, estimated glomerular filtration rate; BMI, body mass index; AF, atrial fibrillation.

Conclusions

Subclinical hypothyroidism was associated with increased cardiovascular events in patients with HFpEF. Elevation of the TSH level was an independent predictor of adverse cardiovascular events.

Acknowledgments

This paper has been uploaded to Research Square as a preprint: [https://assets.researchsquare.com/files/rs-2887595/v1/cbc7cceb-ba45-4137-9808-4a0767587cea.pdf?c=1688998456].

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Disclosure

The authors report no conflicts of interest in this work.

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