Review Article Open Access

Thyroid dysfunction in heart failure with preserved ejection fraction: A systematic review and meta-analysis

Maryam Heidarpour[1]; Mania Banar[1]; Amir Parsa Abhari[2]; Sadegh Mazaheri-Tehrani[2-4]; Ziba Farajzadegan[5]; Mohammad Fakhrolmobasheri[2*]; Parastesh Rezvanian[1]; Davood Shafie[2*]

1- Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
2- Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
4- Student Research Committee, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
5- Community and Preventive Medicine Department, Medicine Faculty, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence:

Mohammad Fakhrolmobasheri;
Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran;
Email: mohammad.fkhr77@gmail.com

Davood Shafie;
Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran;
Email: d.shafe87@gmail.com

Received: 2025-06-04
Accepted: 2025-10-19

How to cite this article:
Heidarpour M; Banar M; Abhari AP; Mazaheri-Tehrani S; Farajzadegan Z; Fakhrolmobasheri M; Rezvanian P; Shafie D. **Thyroid dysfunction in heart failure with preserved ejection fraction: A systematic review and meta-analysis.** ARYA Atheroscler. 2025; 21(6): 80-98.

DOI:
https://doi.org/10.48305/arya.2025.45322.3064

Abstract

BACKGROUND: Despite controversial findings regarding the association between thyroid hormones and heart failure with preserved ejection fraction (HFpEF), thyroid dysfunction is widely assumed to be independently associated with this condition. Herein, we sought to systematically review the existing literature and estimate the prevalence of thyroid dysfunction in patients with HFpEF.

METHODS: We conducted a comprehensive search in PubMed, Scopus, Web of Science, Embase, and ProQuest up to the end of November 2024. Observational studies assessing thyroid dysfunction prevalence in patients with HFpEF were included in this study. The prevalence of overt thyroid dysfunction, low T3 syndrome, and subclinical hypothyroidism (SCH) was pooled using a random-effects model. Duval and Tweedie's Trim and Fill test, funnel plot, and Egger's test were utilized for publication bias assessment. All analyses were conducted with R Version 4.5.1 and Comprehensive Meta-Analysis Version 3 software.

RESULTS: Fourteen studies involving 3,931 subjects with HFpEF were included in this analysis. The pooled prevalence of overt thyroid dysfunction, based on six studies, was 15% (95% CI: 7%–29%). The pooled prevalence of low T3 syndrome was 22% (95% CI: 20%–25%), and for SCH, it was 15% (95% CI: 1%–68%).

CONCLUSION: Despite heterogeneity among the included studies, our findings suggest that thyroid dysfunction is relatively common in patients with HFpEF and may be associated with more severe symptoms and worse outcomes.

Keywords: Thyroid Dysfunction, Heart Failure with Preserved Ejection Fraction, Subclinical Hypothyroidism, Prevalence, Thyroid Hormones

Introduction

Heart failure (HF) is one of the major causes of mortality, morbidity, and health expenditure worldwide[1-3]. Up to 50% of patients suffering from HF symptoms have normal (≥50%) left ventricle ejection fraction (LVEF)[4]. HF with preserved ejection fraction (HFpEF) is defined as the presence of the signs and symptoms of HF alongside a normal EF, which is commonly accompanied by diastolic dysfunction[4]. In contrast to the conventional treatments for HF with reduced ejection fraction (HFrEF), management strategies of HFpEF are yet to be proven beneficial in reducing mortality and morbidity[5]. Although the role of ischemic heart disease (IHD) in developing HFpEF is noticeable, IHD is less prevalent in HFpEF patients than HFrEF[6]. Instead, patients with HFpEF generally suffer from a more serious burden of comorbidities. Obesity, hypertension (HTN), diabetes mellitus (DM), chronic obstructive pulmonary diseases (COPD), atrial fibrillation (AF), chronic kidney disease (CKD), and older age are the best-known comorbidities associated with HFpEF[7]. Another comorbidity, which is somehow less considered, is thyroid dysfunction[8]. The prevalence of thyroid dysfunction in the general population varies from below 1% to up to 5%, according to the type of thyroid disorder and the characteristics of the studied population[9,10]. When it comes to patients with HFpEF, although controversial, the prevalence of thyroid dysfunction is reported to be up to 18%, which could be categorized into hyperthyroidism, clinical and subclinical hypothyroidism (SCH), and low levels of serum triiodothyronine (T3)[11-13]. Although thyroid hormone imbalances could induce HFrEF and diastolic dysfunction, the main aspect of HFpEF is reported to be associated with hypo- and hyperthyroid states[14,15].

Apart from diastolic dysfunction, thyroid dysfunction may lead to the development of other comorbidities associated with HFpEF, such as HTN, obesity, and AF[16-18]. In this regard, studies have proposed thyroid dysfunction, particularly SCH, as comorbidities and potential treatment targets in patients with HFpEF[19-21]. Furthermore, a dysfunctional thyroid could independently predict worse outcomes in HFpEF patients. Also, in the general population, thyroid dysfunction could predict the incidence of HFpEF[22,23]. Accordingly, thyroid dysfunction might need to be considered a more serious and prevalent comorbidity in patients with HFpEF. However, the reports regarding the prevalence and impact of thyroid dysfunction in HFpEF are conflicting. Thus, in this study, we attempt to systematically review the available literature surrounding the prevalence of thyroid dysfunction in HFpEF, the prognostic role of thyroid dysfunction, and the distribution of different subtypes of thyroid dysfunction (including hypo- and hyperthyroidism, SCH, and low T3 syndrome) among patients with HFpEF.

Method

Protocol and registration

This study was conducted and reported according to the instructions provided by the Cochrane Handbook of Systematic Reviews, Joanna Briggs Institute (JBI) Manual for Evidence Synthesis, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[24-26]. The study protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) with code CRD42022360165. The protocol of this study has been approved by the ethics committee of Isfahan University of Medical Sciences.

Review questions

The population of interest is patients with HFpEF. The condition investigated is thyroid disorders, including clinical and subclinical hypo- and hyperthyroidism and low T3 syndrome. According to our hypothetical framework, thyroid dysfunction may affect the intermediate outcomes, including New York Heart Association (NYHA) functional class, quality of life, level of N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP), or incidence of renal failure. Furthermore, we may observe the association of thyroid dysfunction

with main outcomes, including hospitalization and mortality, and thyroid dysfunction may be considered a prognostic factor for the incidence of the main outcomes. Moreover, thyroid dysfunction may be associated with a greater burden of comorbidities and adverse predictive factors, including HTN, obesity, DM, COPD, and AF. This study investigates the prevalence of thyroid dysfunction (E) in patients with HFpEF (P) and its potential impact on clinical outcomes (O). Figure 1 demonstrates a concept map for this framework. Accordingly, the review questions were designed as follows:

- What is the prevalence of clinical and subclinical hypo- and hyperthyroidism and low T3 syndrome in patients with HFpEF?
- How is the association of thyroid dysfunction

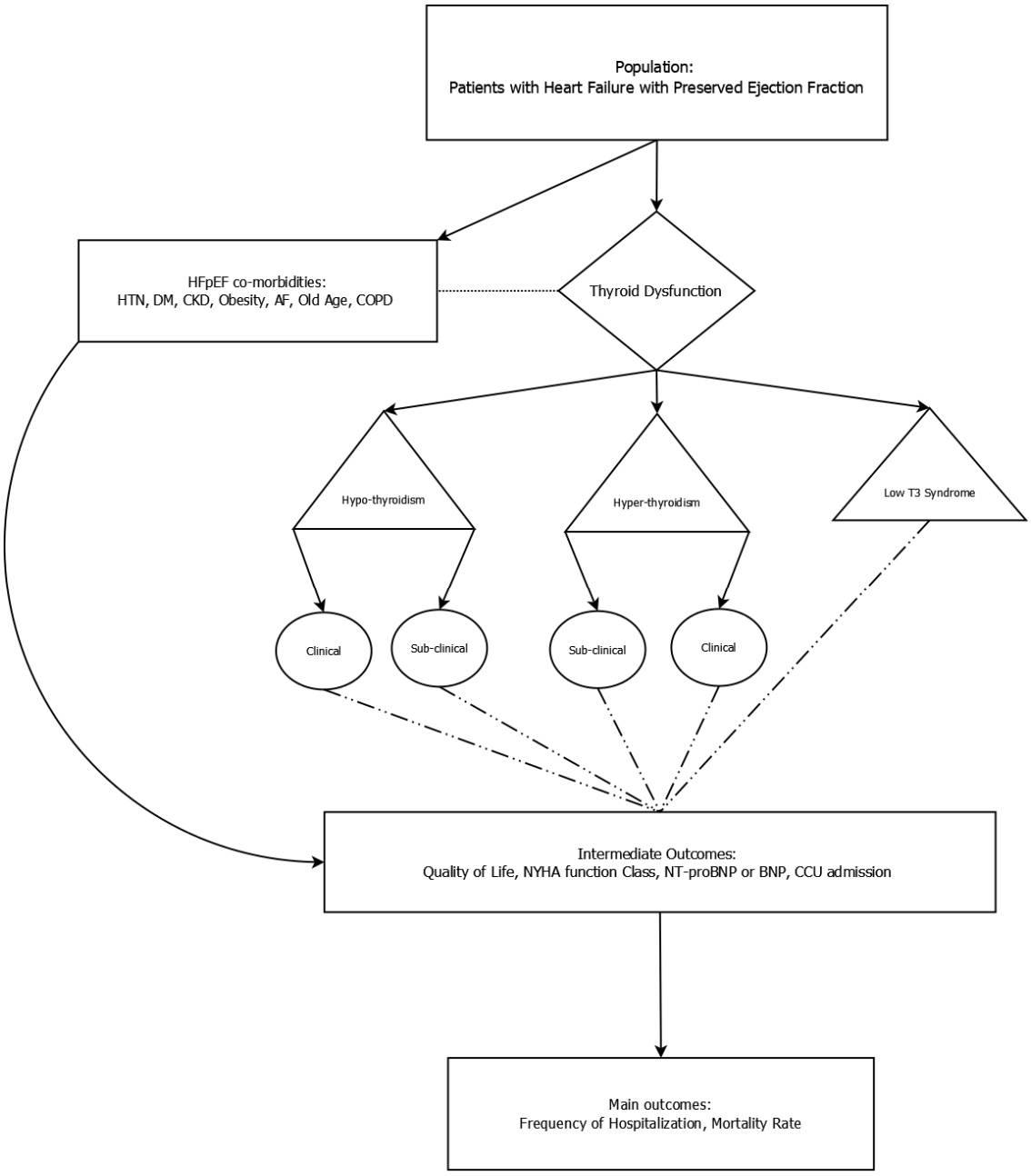

Figure 1. A concept map for review questions.

with intermediate outcomes, including NYHA functional class, quality of life, and level of NT-proBNP in patients with HFpEF?

• What is the effect of thyroid dysfunction on the prognosis of HFpEF regarding the incidence of the main outcomes, including hospitalization and death?

• Is there any association between thyroid dysfunction and the presence and severity of other comorbidities and adverse predictive factors in patients with HFpEF?

Search Strategy

We performed a systematic search in PubMed, Scopus, Web of Science, Embase, and ProQuest without time or country restrictions using the following search line: "Heart failure with preserved ejection fraction" AND (thyroid OR "thyroid gland" OR "T4 hormone" OR "levothyroxine" OR tetraiodothyronine OR T3 OR triidothryonine OR T4 OR thyroxine OR tyroxine OR "T3 hormone" OR triiodothyronine OR liothyronin OR liothyronine OR lyothyronin OR lyothyronine OR T3 OR triiodothyronin OR hypothyroidism OR hyperthyroidism)* up to the end of November 2024. The details of the search string were summarized in Supplementary File 1. The search terms were restricted to the titles, abstracts, and keywords in all databases. We restricted our search results to articles written in the English language. We further screened the reference lists of all included studies. In order to assess the grey literature, the results of the first 10 pages of Google Scholar were also screened. In addition, the databases were manually screened by two authors independently (M.B. and P.R.). After removing duplicate records, the included studies were primarily reviewed by P.R. and Z.F., independently, concerning the relevance of the title and abstract to the aims of the review. The full texts of the potentially relevant articles were further retrieved. We contacted the corresponding authors of the studies with unavailable full texts, requesting them to provide the full texts. The included papers were eventually reviewed by M.B. and M.F., considering the details of the inclusion and exclusion criteria of the review. In this review, archiving, duplicate removal, and management of the group library were performed using EndNote Reference Manager software.

Eligibility criteria and study selection

Observational studies, including cohort, case-control, and cross-sectional studies surrounding the prevalence, prognosis, and clinical outcomes of thyroid dysfunction in patients with HFpEF, were included in our review. Case reports, clinical trials, animal studies, conference abstracts, brief reports, and review articles were excluded. Studies reporting the incidence or prevalence of HFpEF in patients with thyroid dysfunction were excluded. We also excluded studies evaluating thyrotoxic cardiomyopathy or hypothyroid cardiomyopathy. The study selection process was performed in two steps: one using the study's title and abstract, and one using the full text of the studies. M.B. and M.F. independently performed the study selection process, and the debated points were discussed in a team meeting with Z.F., A.P.A., and D.S.

Data extraction

Two reviewers performed the data extraction process independently (S.M-T and A.P.A.). Data regarding the baseline characteristics of the HFpEF population (including mean ± standard deviation [SD] of age, BMI, BNP or NT-proBNP, and number of participants with AF, DM, CKD, COPD, HTN, and anemia) in each study were extracted. Furthermore, available data about the prevalence of thyroid dysfunction (or subtypes of thyroid dysfunction), intermediate outcomes (NYHA functional class, BNP or NT-proBNP, quality of life, hospital readmission, and CCU admission), and main outcomes (hospitalization and mortality) were extracted from each study. We also extracted data on the association between thyroid dysfunction and comorbidities, as well as adverse prognostic factors in HFpEF, including a higher E/E ratio, atrial fibrillation (AF), hypertension (HTN), advanced age, obesity, and chronic kidney disease (CKD). These associations were analyzed in studies in which

the population was categorized according to the presence or subtypes of thyroid dysfunction.

Quality assessment

For studies reporting data regarding the prevalence of overt thyroid dysfunction (which we planned to include in the meta-analysis of prevalence), we used the JBI tool for critical appraisal of studies reporting prevalence. This checklist is composed of nine questions assessing the sampling method, methods of measuring the evaluated condition, statistical analysis, and response rate of the study[27]. For cohort studies, this checklist includes eleven questions addressing the similarity between study groups, sampling method, methods of measuring the exposure, study follow-up, methods of outcome ascertainment, and statistical analysis[28]. Accordingly, for analytical cross-sectional studies, this checklist consists of eight questions addressing the study sampling and setting, methods for assessing the outcomes of interest and confounding factors, and statistical analysis[28]. All of the JBI critical appraisal tools are answered through four options: "yes," "no," "unclear," and "not applicable"[28]. We calculated a standardized quality score for each study by dividing the sum of the scores associated with domains of each checklist (Yes = +1, No = -1, Unclear = 0) by the number of questions in that checklist. The quality assessment process was performed by two independent reviewers (S.M-T and A.P.A.). Any discrepancies were resolved by consensus with a third reviewer (M.H.).

Statistical analysis

Regarding the considerable heterogeneity among studies, a narrative synthesis of results was performed for intermediate and main outcomes. Furthermore, we performed a narrative synthesis of results for the association of comorbidities and negative prognostic factors in HFpEF with thyroid dysfunction. We used the metaprop function from the meta package with the Hartung-Knapp adjustment method to calculate the pooled prevalence and its 95% confidence interval (CI). Given the high methodological and statistical heterogeneity across the studies, we used the random-effects model. Publication bias was evaluated using a funnel plot and Duval and Tweedie's Trim and Fill test. All analyses were performed using R Version 4.5.1 and Comprehensive Meta-Analysis Version 3 software.

Results

Study selection

As demonstrated in Figure 2, the systematic search in databases resulted in 380 records, which were reduced to 222 records after removing duplicate results, of which 24 were considered potentially relevant after screening the titles and abstracts of the studies. From the 24 retrieved full-text articles, four were review articles, one study evaluated the incidence of HFpEF in patients with thyroid dysfunction, one was a case series, one study compared the dose of levothyroxine in hypothyroid patients with and without HF, one study was about thyrotoxic cardiomyopathy, two studies evaluated echocardiographic parameters in patients with thyroid dysfunction, and two studies did not divide the HF population according to EF. Two studies were included during citation searching and grey literature screening in Google Scholar. Eventually, 14 studies included in this review underwent the data extraction and quality assessment process[11,12,23,29-39].

Study characteristics

The summary of the included studies is demonstrated in Table 1. Overall, 3,931 patients with HFpEF participated in the included studies. Regarding study design, ten studies were cross-sectional[11,29-32,34-37,39], and four were cohort[12,23,33,38]. Six studies (1,176 patients) from the 14 included articles reported the prevalence of overt thyroid dysfunction in the HFpEF population[12,29-32,39], which were included in the meta-analysis. In line, four studies (678 patients) reported the prevalence of low T3 syndrome in HFpEF patients, which were included in the meta-analysis for the prevalence of low T3 syndrome in HFpEF patients[11,12,32,38].

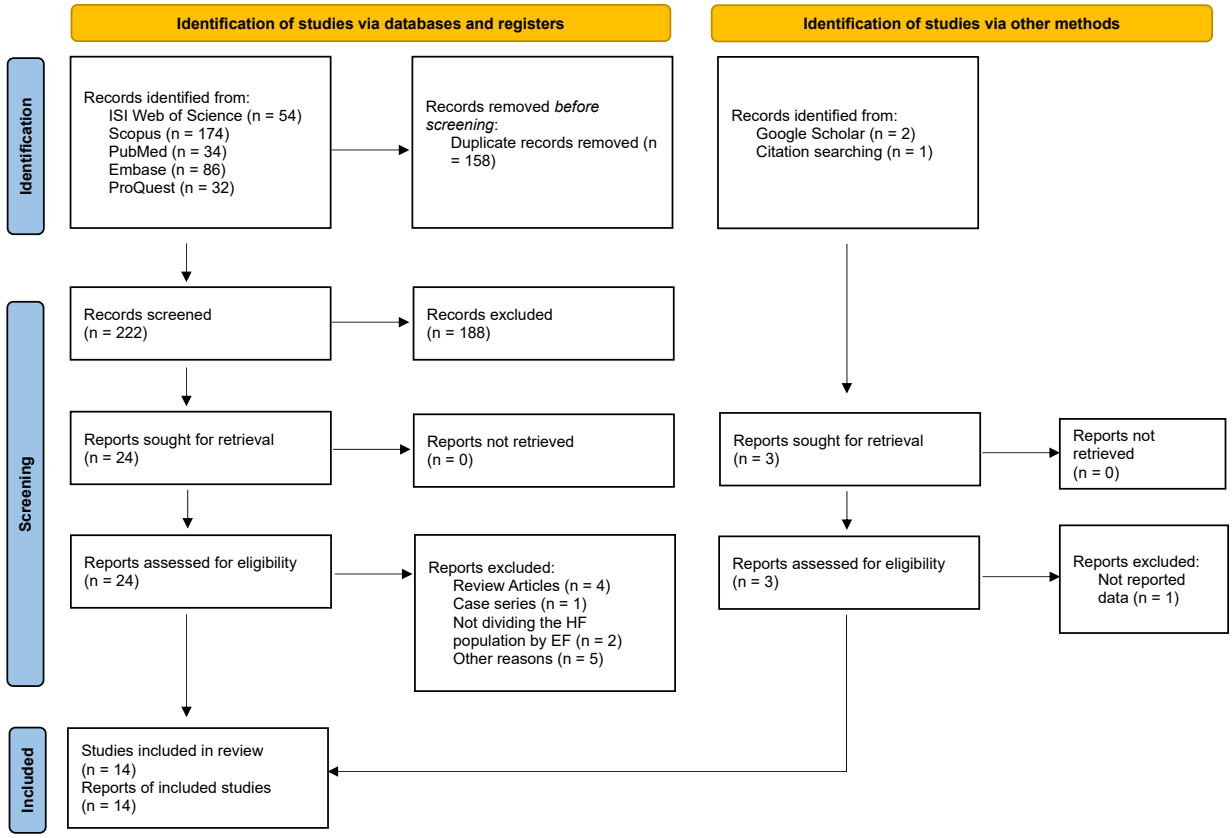

Figure 2. PRISMA flow diagram demonstrating study selection.

Moreover, three studies (1,396 patients) reported the prevalence of SCH among patients with HFpEF[23,32,33]. The intermediate outcomes in HF, including quality of life, NYHA functional class, serum levels of BNP or NT-proBNP, and echocardiographic parameters, were reported in four studies[11,12,23,34]. Furthermore, four studies reported the main outcomes, including hospitalization and mortality in HFpEF patients with different types of thyroid dysfunction[12,23,33,38]. Table 2 demonstrates the quality score associated with each study evaluated by the JBI's critical appraisal tools. The median quality score was 77%. The highest quality score was reported by Sato et al., and the study by Mohamud et al. received the lowest quality score[31,38]. Eight studies were evaluated by the JBI tool for critical appraisal of prevalence studies, two were evaluated by the JBI checklist for cohort studies, and four were evaluated by the tool for analytical cross-sectional studies.

Prevalence of overt thyroid dysfunction

The greatest prevalence was reported in the study by Rywik et al., in which the prevalence of thyroid disease was 34.7% in a sample population of 662 individuals with HFpEF. On the other hand, the smallest proportion of patients with overt thyroid dysfunction was reported to be 5% (two patients with hypothyroidism) in the study by Favuzzi et al., in a small sample size of 40 patients with HFpEF. Figure 3 demonstrates the forest plot of pooled prevalence of overt thyroid dysfunction in HFpEF patients. Results from random-effects analysis indicated the estimated pooled prevalence as p = 0.15 [0.07–0.29]. Sensitivity analyses were performed by removing the studies with a non-adequate sample size (Favuzzi et al. and Agrawal et al.)[29,32]. Accordingly, the pooled prevalence increased to p = 0.20 [0.09–0.38] (Figure 4). Furthermore, findings from the funnel plot, Egger's test, and Duval and Tweedie's Trim and Fill test indicated

Table 1. Baseline characteristics of the included studies.

First author (year)	Region	HFpEF population									Reported outcomes	Results
		556(Female=46%), HFpEF definition: HF patients with EF ≥50% based on ESC HF guidelines									Prevalence: overt thyroid dysfunction	17.4%
		Obesity	CKD	COPD	Anemia	NT-proBNP(ng/l)	Age	HTN	DM	AF		
Koen W. Streng(2018)	Europe	235	312	132	253	1559 [511–3998]	78 ± 9.8	386	198	275	Intermediate outcome: Quality of life in patients without and with thyroid dysfunction, respectively	KCCQ overall score: 39 [24–55] Vs 34 [21–48] 0.017, P<0.05 EQ-5D VAS score: 55 [45–70] Vs 50 [41–60], P<0.05
											Main outcome: All-cause mortality, Hospitalization	All-Cause mortality: HR= 1.42[1.01,2.00] Hospitalization: HR= 1.52[1.06,2.18]
		HFpEF population										
		89 (Female= 69%), HFpEF definition: Patients with EF ≥50% and who meet Framingham criteria for HF									Prevalence: low T_3, elevated T_3, low free T_4, elevated free T_4, low TSH, elevated TSH	low T_3: 22% elevated T_3: 3% low free T_4: 7% elevated free T_4: 2% low TSH: 13% elevated TSH: 10%
		Obesity	CKD	COPD	Anemia	BNP(pg/ml)	Age	HTN	DM	AF		NYHA FC 1&2 / 3&4: 28/18 vs 15/28, P<0.05
Senthil Selvaraj (2012)	USA	53	35	21	N/A	214 (66–603)	67± 14	73	28	23	Intermediate outcome: NYHA function class, BNP, Echocardiography parameters between patients with T_3(ng/dl), ≥108 and <108, respectively	BNP: 133 (46–318) vs 326 (115–874), p<0.05 Echocardiography E velocity(cm/s): 93±27 vs 110±36, P<0.05 E deceleration time (ms): 231±47 vs 206±47, p<0.05 **Other parameters were not significantly different between groups**
YU SATO(2019)	Japan	HFpEF population 513, HFpEF definition: HF patients with EF ≥50%									Main outcome: Prevalence : Low T_3 syndrome in patients with HFpEF	N/A 116(32%)
		Obesity	CKD	COPD	Anemia	BNP	Age	HTN	DM	AF		

Table 1. Baseline characteristics of the included studies.

First author (year)	Region	HFpEF population									Reported outcomes	Results
											Intermediate outcome:	N/A
		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Main outcome: all-cause and cardiac mortality in low T_3 vs normal T_3	All-cause mortality: HR=2.388 [1.556-3.666] Cardiac mortality: HR= 2.045 [0.961-4.352]
Salzano (2016)	Europe	HFpEF population 36, HFpEF definition: HF patients with EF ≥50% based on ESC HF guidelines									Prevalence: Low T_3 syndrome in patients with HFpEF	6 (16%)
		BMI	CKD	COPD	Anemia	BNP	Age	HTN	DM	AF	Intermediate outcome:	N/A
		29 ± 4	N/A	N/A	N/A	N/A	66 ± 14	80%	51 %	58%	Main outcome:	N/A
		HFpEF population									Prevalence: Subclinical hypothyroidism in patients with HFpEF	63(5.69%)
		1107, HFpEF definition: HF patients with EF ≥40%										CCU admission: 7 (11.1%) Vs 131 (12.5%) 1 month readmission23 (36.50%) vs 322 (31%) 3 months readmission: 17 (27%) Vs 278 (26.6%) 6 months readmission: 10 (15.9%) Vs 233 (22.3%)
Saad(2020)	USA	BMI	CKD	COPD	Anemia	BNP	Age	HTN	DM	AF	Intermediate outcomes : CCU admission, readmission in 1, 3, and 6 months in SCH vs non SCH patients with HFpEF	
		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Main outcome: one year mortality in SCH vs non SCH patients with HFpEF	One year mortality: 6(9.5%) vs 80(7.7%)
		HFpEF population									Prevalence: thyroid dysfunction in patients with HFpEF	Thyroid dysfunction including SCH and low T_3 syndrome : 25(24.27%)
Abdullahi Mohamud(2022)	Africa	103, HFpEF definition: HF patients with EF ≥50%									Intermediate outcomes:	N/A
		BMI	CKD	COPD	Anemia	BNP	Age	HTN	DM	AF		
		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Main outcome:	N/A

Table 1. Baseline characteristics of the included studies.

First author (year)	Region	HFpEF population																		Reported outcomes	Results
Yusuf Mohamud(2022)	Africa	HFpEF population 74 (female= 44.6%), HFpEF definition: HF patients with EF ≥50%																		Prevalence: prevalence of thyroid disease in patients with HFpEF Intermediate outcomes: Main outcome:	13(17.6%) N/A N/A
		BMI		CKD		COPD		Anemia		BNP		Age		HTN		DM		AF			
		N/A		N/A		N/A		N/A		N/A		63.5±13.6		61		16		N/A			
Meng(2020)	China	HFpEF population 146, HFpEF definition: HF patients with EF ≥50%																		Prevalence: Intermediate outcomes: BNP, echocardiographic parameters in HFpEF patients with and without SCH Echocardiography: E/A: 0.873 ± 0.202 vs 0.939 ± 0.199 E/E': 10.93 ± 1.97 vs 8.97 ± 1.61 Main outcome:	N/A BNP(pg/ml) : 210.45 ± 52.42 vs 188.75 ± 49.08 N/A
		BMI		CKD		COPD		Anemia		BNP(pg/ml)		Age		HTN		DM		AF			
		euT	SCH	euT	SCH	euT	SCH	euT	SCH	euT	SCH	euT	SCH	euT	SCH	euT	SCH	euT			
		22.74 ± 2.99	23.08 ± 2.41	N/A	N/A	N/A	N/A	N/A	N/A	188.75 ± 49.08	210.45 ± 52.42	66.85 ± 7.59	68.99 ± 8.24	42	38	12	14	N/A			
Rywik(2022)	Poland	HFpEF population 662(female=56%), HFpEF definition: HF patients with EF ≥50%																		Prevalence: thyroid disease in patients with HFpEF Intermediate outcomes: Main outcome:	230(34.7%) N/A N/A
		BMI		CKD		COPD		Anemia		NT-proBNP(pg/ml)		Age		HTN		DM		AF			
		N/A		244		187		169		1446 (509.8–3689)		70.5 (60.1–80.4)		576		222		427			
Hassan(2016)	USA	HFpEF population 249(female=56.6%), HFpEF definition: HF patients with EF ≥50%																		Prevalence: prevalence of SCH among patients with HFpEF Intermediate outcomes:	71(28.5%) N/A

Table 1. Baseline characteristics of the included studies.

First author (year)	Region	HFpEF population									Reported outcomes	Results
Favuzzi (2020)	Italy	BMI	CKD	COPD	Anemia	BNP(ng/l)	Age	HTN	DM	AF	Main outcome: mortality rate among HFpEF patients with and without SCH (follow-up = 8.75 ± 0.17 years)	29.6% Vs 14.9%
		32.16±10.85	N/A	N/A	N/A	587.27±726.99	72.15±13.40	N/A	N/A	N/A		
		HFpEF population 40(Female=32.5%), HFpEF definition: HF patients with EF ≥50%									Prevalence: prevalence of Low T_3 syndrome, SCH, hypothyroidism and subclinical hyperthyroidism in patients with HFpEF	Low T_3 syndrome: 9(22.5%) SCH: 8(20%) Hypothyroidism: 2(5%) subclinical hyperthyroidism: 4(10%)
											Intermediate outcomes:	N/A
		BMI	CKD	COPD	Anemia	NT-proBNP(ng/ml)	Age	HTN	DM	AF	Main outcome:	N/A
		28.22±24.96	N/A	22	31	2726.33±2662.03	78.33±8.05	34	18	17		
Aizpurua(2021)	Netherlands	HFpEF population 300(Female: 66.3%), HFpEF definition: HF patients with EF ≥50% based on ESC HF guidelines									Prevalence: prevalence of thyroid diseases in HFpEF patients	38(12.6%)
											Intermediate outcomes:	N/A
		BMI	CKD	COPD	Anemia	NT-proBNP(ng/ml)	Age	HTN	DM	AF	Main outcome:	N/A
		N/A	115	46	106	N/A	N/A	257	99	169		
Agrawal (2021)	India	HFpEF population 100(Female: 62%), HFpEF definition: Patients with EF ≥50% and who meet Framingham criteria for HF									Prevalence: prevalence of hypothyroidism in HFpEF patients	6(6%)
											Intermediate outcomes:	N/A
		Overweight/obesity	CKD	COPD	Anemia	NT-proBNP(ng/ml)	Age	HTN	DM	AF	Main outcome:	N/A
		80	2	N/A	76	N/A	>61 : 44 <60 : 56	82	28	8		
Mfeuke u-Kuate(2021)	Cameroon	HFpEF population 30, HFpEF definition: HF patients with EF ≥50%									Prevalence: hyperthyroidism and hypothyroidism in patients with HFpEF	Hyperthyroidism(including clinical and subclinical) : 4(13.3%) Hypothyroidism (including subclinical and low t_3 syndrom) : 9(33.3%)

Table 1. Baseline characteristics of the included studies.

First author (year)	Region	HFpEF population									Reported outcomes	Results
		BMI	CKD	COPD	Anemia	NT-proBNP(ng/ml)	Age	HTN	DM	AF		
		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Intermediate outcomes:	N/A
											Main outcome:	N/A

Table 2. Quality assessment of the included studies using JBI tool.

First author	Critical appraisal tool	Raw Score	Standardized score
Agrawal	JBI check list for critical appraisal of prevalence studies	6/9	66%
azipurua	JBI check list for critical appraisal of prevalence studies	7/9	77%
favvuzi	JBI check list for critical appraisal of prevalence studies	8/9	88%
Hassan	JBI check list for critical appraisal of cohort studies	5/11	45%
Meng	JBI check list for critical appraisal of cross sectional studies	7/8	87%
Mfeukeu	JBI check list for critical appraisal of cross sectional studies	6/8	75%
Yusuf Mohamud	JBI check list for critical appraisal of prevalence studies	4/9	44%
Abdullahi mohamud	JBI check list for critical appraisal of cross sectional studies	6/9	66%
Rywik	JBI check list for critical appraisal of prevalence studies	7/9	77%
Saad	JBI check list for critical appraisal of cohort studies	8/11	72%
salzano	JBI check list for critical appraisal of cross sectional studies	6/8	75%
sato	JBI check list for critical appraisal of prevalence studies	9/9	100%
selvaraj	JBI check list for critical appraisal of prevalence studies	8/9	88%
streng	JBI check list for critical appraisal of prevalence studies	7/9	77%

Raw score is calculated as the sum of scores attributed to the answer of each study. Yes = +1, unclear = 0, No = -1
Standardized Score (%): Raw score / maximum score in the particular checklist * 100

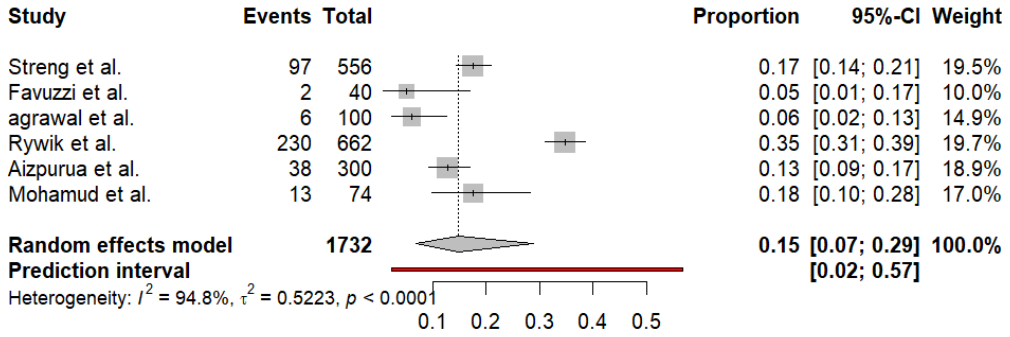

Figure 3. Forest plot of pooled prevalence of overt thyroid dysfunction

no significant publication bias (Egger's test p-value = 0.32) (Supplementary File 2).

Prevalence of Low T3 syndrome

As shown in Figure 5, four studies investigating 678 patients were included in the fixed-effects model analysis, indicating the pooled prevalence of low T3 syndrome as p = 0.22 [0.20–0.25]. Egger's test for publication bias indicated no considerable bias; however, Duval and Tweedie's Trim and Fill test indicated that one study was missing to the left of the mean, decreasing the pooled prevalence to p = 0.213 [0.191–0.236] (Supplementary File 3).

Prevalence of subclinical hypothyroidism

Random-effects model analysis indicated the pooled prevalence of SCH as p = 0.15 [0.01–0.68] (Figure 6). Moreover, tests for publication bias indicated no considerable publication bias.

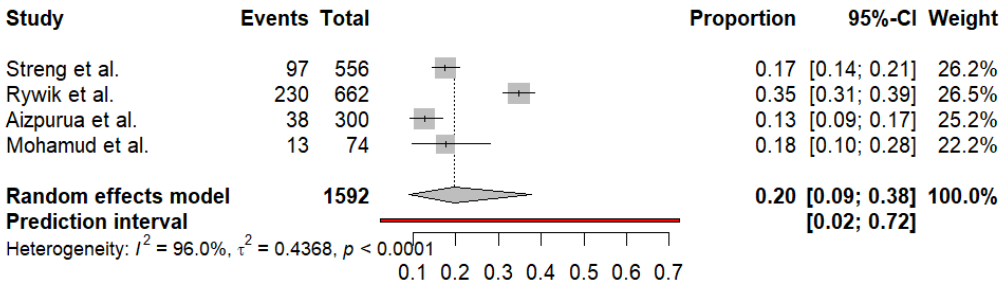

Figure 4. Forest plot of pooled prevalence of overt thyroid dysfunction after excluding studies with non-adequate population.

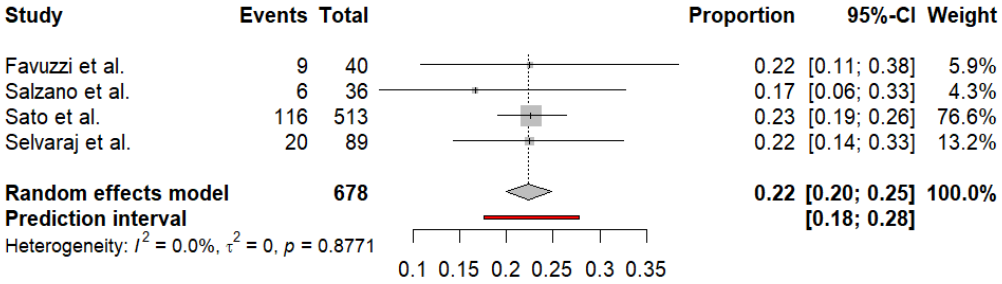

Figure 5. Forest plot of pooled prevalence of low T_3 syndrome.

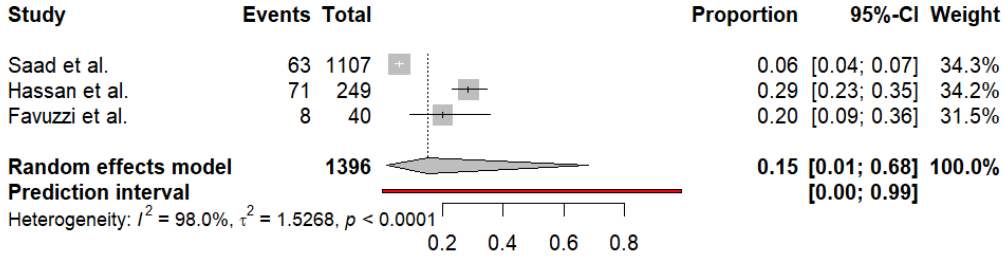

Figure 6. Forest plot of pooled prevalence of subclinical hypothyroidism.

Association between thyroid dysfunction and intermediate outcomes in HFpEF

Streng et al. evaluated the association between thyroid dysfunction and quality of life in patients with HFpEF. The overall Kansas City Cardiomyopathy Questionnaire (KCCQ) score was significantly lower in patients with thyroid dysfunction than in those without thyroid dysfunction: 34 [21–48] vs. 39 [24–55], P = 0.017, P-value < 0.05. Similarly, the EQ-5D VAS score was significantly lower in HFpEF patients with thyroid dysfunction compared to individuals without thyroid dysfunction: 55 [45–70] vs. 50 [41–60], P-value < 0.05[12]. Selvaraj et al. indicated that HFpEF patients with T3 lower than 108 ng/dl had higher NYHA functional classification, serum BNP, E velocity, and lower E deceleration time[11]. In line, the study by Meng et al. demonstrated a significantly higher level of serum BNP, lower E/A, and higher E/E' ratio[34].

Association between thyroid dysfunction and main outcomes in HFpEF

Streng et al. indicated that HFpEF patients with thyroid dysfunction had 1.52 [1.06–2.18] and 1.42 [1.01–2.00] fold higher risks for hospitalization and mortality, respectively, compared to HFpEF patients without thyroid

Table 3. Studies comparing prevalence of common predictive factors for the outcomes between those with and without thyroid dysfunction.

First author	HFpEF population		AF	Age	HTN	Pulmonary HTN	E/E'	BMI	DM	COPD	CKD
Selvaraj (2012)	89	$T_3 \geq 108$ ng/dl (n=46)	10 (22%)	63 ± 14	36 (78%)	N/A	15.5 ± 6.2	34.0 ± 9.0	9 (20%)	10 (22%)	14 (30%)
		$T_3 < 108$nd/dl (n=43)	13 (30%)	70 ± 13	37 (86%)	N/A	18.2 ± 10.4	32.0 ± 7.5	19 (44%)	11 (26%)	21 (49%)
Meng (2020)	146	Euthyroidisim	N/A	66.85 ± 7.59	42	N/A	8.97 ± 1.61	22.74 ± 2.99	12	N/A	N/A
		Subclinical hypothyroidism	N/A	68.99 ± 8.24	38	N/A	10.93 ± 1.97	23.08 ± 2.41	14	N/A	N/A

dysfunction[12]. Hassan et al., in a retrospective cohort study with a mean follow-up period of 8.75 years on 249 HFpEF patients, indicated a significantly higher mortality rate in patients with SCH (29.6% vs. 14.9%, P-value < 0.05)[33]. On the contrary, the study by Saad et al. on 1,107 HFpEF patients reported no significantly higher risk of hospitalization at 1, 3, and 6 months, and no significantly higher one-year mortality in HFpEF patients with SCH compared to patients without SCH[23].

Association between thyroid dysfunction and predictive factors in HFpEF

Only two studies have compared the prevalence or severity of common predictive factors for outcomes between HFpEF patients with and without thyroid dysfunction (Table 3)[11,34]. Selvaraj et al., in a study on HFpEF patients, compared the prevalence of HTN, CKD, COPD, DM, and AF between 43 patients with T3 < 108 ng/dl and 46 patients with T3 ≥ 108 ng/dl. The results indicated that DM was the only comorbidity associated with T3 < 108, whereas the prevalence of other factors, as well as the mean ± SD of age, BMI, and E/E' ratio, did not differ significantly between the two study groups. The other study by Meng et al. compared the prevalence of HTN and DM between HFpEF patients with and without SCH; the authors further compared the mean ± SD of age, BMI, and E/E' ratio between the study groups. The results of their study indicated that HFpEF patients with SCH had a higher E/E' ratio than those without SCH.

Discussion

In this systematic review and meta-analysis, we gathered data from 14 studies on a total population of 3,931 patients with HFpEF. According to the meta-analysis results, the pooled prevalence of overt thyroid dysfunction was p = 0.15 [0.07–0.29]. Furthermore, our findings indicated that the prevalence of SCH and low T3 were p = 0.15 [0.01–0.68] and p = 0.22 [0.20–0.25], respectively. Nevertheless, these results should be interpreted cautiously, as the total number of included studies in the meta-analysis was relatively small. Also, there was significant heterogeneity. To the best of our knowledge, this is the first systematic review in which thyroid dysfunction and its subtypes were assessed in the context of prevalence, association with comorbidities, and effects on the outcomes of HFpEF. Furthermore, as previous studies have indicated that the H2FPEF score, which includes hypertension, obesity, AF, older age, pulmonary hypertension, and increased ventricular filling pressure (E/E' > 9), is a good prognostic and diagnostic tool for patients with HFpEF, we attempted to investigate the association between thyroid dysfunction and the predictive factors included in the H2FPEF score[40–42]. We observed that patients with SCH

may have a higher E/E' ratio, and individuals with lower T3 were more likely to suffer from DM; however, these findings are limited to the results from only two studies reporting the burden of comorbidities in relatively small sample sizes[11,34].

Animal studies have indicated that not only thyroid dysfunction may be associated with worse cardiovascular outcomes, but also, even in the presence of normal serum levels of thyroid hormones, cardiac tissue hypothyroidism, which is a result of diminished conversion of T4 to T3, may be a key contributor to the development of myocardial dysfunction[20]. From the molecular point of view, the effects of thyroid hormones on cardiac tissue are mediated through genomic and non-genomic pathways. Thyroid hormone receptors (TRs) are the mediators of the genomic effects of T3. As a result of alternative splicing of TRα and TRβ, different isoforms of the TRs are expressed in different tissues; accordingly, TRα-1 is the predominant TR in cardiac tissue[43,44]. The thyroid hormone–thyroid receptor complex affects the expression of certain genes, which are mainly involved in the modulation of cardiac bioenergetics and the production of myofilaments in cardiomyocytes[8]. Particularly, thyroid hormones upregulate the expression of sarcoplasmic/endoplasmic reticulum calcium ATPase 2, Na/K ATPase, β1 adrenergic receptors, matrix metalloproteinases, and voltage-gated potassium channels. These genomic effects are responsible for enhanced intracellular calcium ion kinetics, leading to optimal ventricular contraction and relaxation, an optimal response to the inotropic effects of catecholamine, and diminution in cardiac fibrosis[20]. Thyroid hormones may also affect cardiomyocytes by inhibiting pro-apoptotic pathways[45]. Moreover, thyroid hormones could directly affect mitochondrial function, as TRs are also present in mitochondria[46].

Decreased bioavailability of thyroid hormones in cardiac tissue may be due to disturbed production of T3 and T4 from the thyroid gland or systemic or cardiac-specific overexpression of type 3 deiodinase (which converts T4 into reverse T3) as a response to systemic inflammation. Nevertheless, the diminished effect of thyroid hormones in cardiac tissue could lead to impaired cardiac bioenergetics, impaired cardiac contraction, and, most importantly, impaired ventricular relaxation, the cornerstone of HFpEF[8,20]. On the other hand, overproduction of thyroid hormones leads to disturbed genomic expression of the proteins mentioned above, which could negatively affect cardiac tissue, causing tachycardia and tachycardia-induced cardiomyopathy, arrhythmias—particularly AF—and further development of high-output cardiac failure[13].

Apart from the direct effects of thyroid hormones on cardiac tissue, the association between thyroid hormone disturbances and common comorbidities in HFpEF plays an important role in the pathophysiology of HFpEF. Hypothyroidism is known to be associated with obesity, HTN, and accelerated atherosclerosis[8,17,18]. Furthermore, it has also been demonstrated that hyperthyroidism is associated with HTN and AF[8,47]. Moreover, hypo- and hyperthyroid states could be causes of pulmonary hypertension[48]. In line, a study on patients hospitalized for acute decompensated heart failure due to thyrotoxicosis indicated that HFpEF was the most prevalent type of HF among the patients. Furthermore, the authors indicated that patients with thyrotoxic HF were more likely to have pulmonary hypertension and right HF[49].

Regarding diastolic dysfunction, a study on 25 hyperthyroid patients indicated that hyperthyroidism might not induce diastolic dysfunction at rest or during exercise echocardiography[50]. In contrast, clinical studies have established the role of subclinical and clinical hypothyroidism in developing diastolic dysfunction[19]. Selvaraj et al., in a study on 89 consecutive HFpEF patients, demonstrated that a T3 hormone level lower than 108 ng/dl was associated with severe diastolic dysfunction and higher BNP levels compared to patients with T3 higher than 108 ng/dl (normal serum T3 range was defined as 178 > T3 > 87 in their study)[11].

Regarding the prognosis of HFpEF, a study on 249 patients with HFpEF with a mean follow-up time of 8.75 years indicated that SCH was an independent predictor of mortality (29.6% vs. 14.9%, mortality rate in patients with and without SCH, respectively)[33]. In contrast, the study by Saad et al. reported no significant association between SCH and mortality, CCU admission, and rehospitalization in patients with HFpEF; however, the authors mentioned that those findings may be limited, as the data regarding readmission and death were collected retrospectively from a single medical center[23].

Taken together, despite the limited results in this field, our findings indicated that the prevalence of thyroid dysfunction in patients with HFpEF is considerably higher compared to the general population. Furthermore, regarding the incidence of outcomes, we observed that the HFpEF population with SCH and low T3 syndrome may experience more severe symptoms of HF and may be at higher risk of hospitalization and mortality. Accordingly, a phase two randomized clinical trial evaluated the effect of supplementation of HF patients with a thyroid hormone analog, namely DITPA (3,5-diiodothyropropionic acid). Although supplementation with DITPA was associated with improved hemodynamic and metabolic parameters, no symptomatic benefit and a relatively high burden of adverse effects were observed[51]. Considering the high prevalence of thyroid dysfunction among HFpEF patients and its adverse effect on the prognosis of HFpEF, we suggest that screening of thyroid function tests in patients with HFpEF warrants further studies on larger populations to investigate approaches to overcome the burden of clinical and subclinical thyroid dysfunction in HFpEF patients.

Conclusion

Thyroid dysfunction is a relatively common comorbidity in patients with HFpEF. Apart from overt thyroid dysfunction, SCH and low T3 syndrome may be associated with a higher burden of comorbidity, more severe symptoms, and worse outcomes in HFpEF patients. Further studies are warranted to investigate potential approaches for the management of clinical and subclinical thyroid dysfunction in this group of patients. Given that our results are derived from a relatively small number of studies, additional research is needed to clarify the prevalence and role of different subtypes of thyroid dysfunction in HFpEF patients. Taken together, our findings highlight an association between thyroid dysfunction and HFpEF, suggesting that evaluation of thyroid function in these patients may be considered in future studies and clinical practice; however, recommendations regarding screening and treatment should await confirmation from larger prospective investigations.

Limitations

This systematic review and meta-analysis has some limitations that should be considered when interpreting the findings. First, although the pooled data involved a substantial number of patients with HFpEF (3,931 subjects), the total number of studies included in the meta-analysis was relatively small, which may limit the generalizability of our results. The heterogeneity observed across the included studies in terms of study design, population, and thyroid dysfunction classification could introduce bias and affect the robustness of our findings. Moreover, the data on comorbidities and clinical outcomes were not consistently reported, and several studies had small sample sizes, limiting our ability to draw strong conclusions regarding the prognostic impact of thyroid dysfunction in HFpEF. Taken together, our findings highlight an association between thyroid dysfunction and HFpEF, but given the cross-sectional nature and limited size of the available evidence, recommendations for routine screening or treatment cannot be firmly established at this stage. Future large-scale prospective studies are warranted to confirm these associations, clarify the prognostic significance of different subtypes of thyroid dysfunction, and explore whether thyroid function assessment could have a role in the clinical management of HFpEF patients.

Conflict of interests
The authors declare no conflict of interest.

Funding
There is no funding in this study.

Author's Contributions
Study Conception or Design: MH, MF, DS
Data Acquisition: MB, APA, SMT, ZF, PR
Data Analysis or Interpretation: SMT, ZF
Manuscript Drafting: MB, APA, SMT, PR
Critical Manuscript Revision: MH, ZF, MF, DS

All authors have approved the final manuscript and are responsible for all aspects of the work.

References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023 Jan 18;118(17):3272-87. https://doi.org/10.1093/cvr/cvac013
2. Namvar M, Fakhrolmobasheri M, Mazaheri-Tehrani S, Heidarpour M, Emamimeybodi M, Shafie D. Association between the Length of Hospital Stay and 30-Day Outcomes in Patients Admitted with Acute Decompensated Heart Failure. Emerg Med Int. 2023 Mar 6;2023:6338597. https://doi.org/10.1155/2023/6338597
3. Rabiee Rad M, Ghasempour Dabaghi G, Sadri H, Darouei B, Amani-Beni R, Mazaheri-Tehrani S. Triglyceride glucose-waist circumference as a predictor of mortality and subtypes of cardiovascular disease: a systematic review and meta-analysis. Diabetol Metab Syndr. 2025 Feb 15;17(1):59. https://doi.org/10.1186/s13098-025-01616-9
4. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res. 2019;124:1598–617. https://doi.org/10.1161/CIRCRESAHA.119.313572
5. Gard E, Nanayakkara S, Kaye D, Gibbs H. Management of heart failure with preserved ejection fraction. Aust Prescr. 2020;43:12–7. https://doi.org/10.18773/austprescr.2020.006
6. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction. Circ Heart Fail. 2017;10:e003875. https://doi.org/10.1161/CIRCHEARTFAILURE.117.003875
7. van Heerebeek L, Paulus WJ. Understanding heart failure with preserved ejection fraction: where are we today? Neth Heart J. 2016;24:227–36. https://doi.org/10.1007/s12471-016-0810-1
8. Yamakawa H, Kato TS, Noh JY, Yuasa S, Kawamura A, Fukuda K, et al. Thyroid hormone plays an important role in cardiac function: from bench to bedside. Front Physiol. 2021;12:606931. https://doi.org/10.3389/fphys.2021.606931
9. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14:301–16. https://doi.org/10.1038/nrendo.2018.18
10. Shekarian A, Fakhrolmobasheri M, Mazaheri-Tehrani S, Yousefian A, Heidarpour M. The prevalence of positive thyroid autoantibodies in patients with subacute thyroiditis: a systematic review and meta-analysis. Endocrine. 2024;84:29–41. https://doi.org/10.1007/s12020-023-03655-6
11. Selvaraj S, Klein I, Danzi S, Akhter N, Bonow RO, Shah SJ. Association of Serum Triiodothyronine With B-Type Natriuretic Peptide and Severe Left Ventricular Diastolic Dysfunction in Heart Failure With Preserved Ejection Fraction. Am J Cardiol. 2012;110:234–9. https://doi.org/10.1016/j.amjcard.2012.02.068
12. Streng KW, Nauta JF, Hillege HL, Anker SD, Cleland JG, Dickstein K, et al. Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction. Int J Cardiol. 2018;271:132-9. https://doi.org/10.1016/j.ijcard.2018.04.001
13. Khatiwada S, Boro H, Farooqui FA, Alam S. Endocrine causes of heart failure: A clinical primer for cardiologists. Indian Heart J. 2021;73:14-21. https://doi.org/10.1016/j.ihj.2020.11.003
14. Tafarshiku R, Henein MY, Berisha-Muharremi V, Bytyçi I, Ibrahimi P, Poniku A, et al. Left Ventricular Diastolic and Systolic Functions in Patients with Hypothyroidism. Medicina (Mex). 2020;56:524. https://doi.org/10.3390/medicina56100524
15. Li H, Zeng R, Liao Y, Fu M, Zhang H, Wang L, et al. Prevalence and Risk Factors of Left Ventricular Diastolic Dysfunction in Patients With Hyperthyroidism. Front Endocrinol (Lausanne). 2021 Jan 8;11:605712. https://doi.org/10.3389/fendo.2020.605712
16. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, et al. Thyroid Function Within

the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. Circulation. 2017 Nov 28;136(22):2100-16. https://doi.org/10.1161/CIRCULATIONAHA.117.028753
17. Yan Y, Xu M, Wu M, Wang X, Li F, Zhang J, et al. Obesity is associated with subclinical hypothyroidism in the presence of thyroid autoantibodies: a cross-sectional study. BMC Endocr Disord. 2022;22:94. https://doi.org/10.1186/s12902-022-00981-0
18. Cai Y, Ren Y, Shi J. Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. Hypertens Res. 2011;34:1098-105. https://doi.org/10.1038/hr.2011.91
19. Kinugasa Y, Yamamoto K. Subclinical hypothyroidism as a new therapeutic target for patients with heart failure with preserved ejection fraction. Circ J Off J Jpn Circ Soc. 2014;78:1333-4. https://doi.org/10.1253/circj.cj-14-0436
20. Neves JS, Vale C, von Hafe M, Borges-Canha M, Leite AR, Almeida-Coelho J, et al. Thyroid hormones and modulation of diastolic function: a promising target for heart failure with preserved ejection fraction. Ther Adv Endocrinol Metab. 2020 Oct 4;11:2042018820958331. https://doi.org/10.1177/2042018820958331
21. Shekarian A, Mazaheri-Tehrani S, Shekarian S, Pourbazargan M, Setudeh M, Abhari AP, et al. Prevalence of subclinical hypothyroidism in polycystic ovary syndrome and its impact on insulin resistance: a systematic review and meta-analysis. BMC Endocr Disord. 2025;25:75. https://doi.org/10.1186/s12902-025-01896-2
22. Inciardi RM, Chandra A, Claggett B, Wijkman M, Selvin E, Kottgen A, et al. Thyroid dysfunction and incident heart failure phenotypes among older adults: the atherosclerosis risk in communities (aric) study. Eur Heart J. 2020;41 Supplement_2:ehaa946.0866. https://doi.org/10.1093/ehjci/ehaa946.0866
23. Saad M, Lacoste AG, Balar P, Zhang A, Vittorio TJ. The subclinical hypothyroid state might predict 30-day readmission in patients admitted with acute heart failure syndrome and reduced left ventricular ejection fraction. Ther Adv Cardiovasc Dis. 2020;14:1753944720977742. https://doi.org/10.1177/1753944720977742
24. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
26. JBI Manual for Evidence Synthesis - JBI Global Wiki. https://jbi-global-wiki.refined.site/space/MANUAL. Accessed 9 Mar 2023.
27. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015 Sep;13(3):147-53. https://doi.org/10.1097/xeb.0000000000000054
28. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiology and risk. Joanna Briggs Inst Rev Man Joanna Briggs Inst. 2017;5.
29. Agrawal BK, Aggarwal G, Gahlawat R, Prasad S, Saini A, Kaur B, et al. A Profile of Heart Failure with Preserved Ejection Fraction in a Teaching Hospital. Bangladesh J Med Sci. 2021;20:39-44. https://doi.org/10.3329/bjms.v20i1.50343
30. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens MTHM, Weerts J, Spanjers MHA, et al. Iron deficiency impacts prognosis but less exercise capacity in heart failure with preserved ejection fraction. Esc Heart Fail. 2021;8:1304–13. https://doi.org/10.1002/ehf2.13204
31. Farah Yusuf Mohamud M, Jeele MOO, Cetinkaya O, Goitom Sereke S, Bongomin F, AM Ahmed M. Baseline Characteristics, Risk Factors and Etiology of Heart Failure Among Patients Hospitalized at a Teaching Hospital in Somalia: Cross-Sectional Study. Res Rep Clin Cardiol. 2022;13:63-71. https://doi.org/10.2147/RRCC.S380136
32. Favuzzi AMR, Venuti A, Bruno C, Nicolazzi MA, Fuorlo M, Dajko M, et al. Hormonal deficiencies in heart failure with preserved ejection fraction: prevalence and impact on diastolic dysfunction: a pilot study. Eur Rev Med Pharmacol Sci. 2020 Jan;24(1):352-61. https://doi.org/10.26355/eurrev_202001_19933
33. Hassan A, Altamiranoufion A, Mahmoud S, Villines D, Mendyuk H, Klein L. Association between Subclinical Hypothyroidism and Cardiovascular Mortality in Patients Suffered from Heart Failure with Preserved Ejection Fraction. J Cardiobiol. 2016;4(1):1-4.
34. Meng Y, Zhao T, Zhang ZY, Zhang DK. Association between sub-clinical hypothyroidism and heart failure with preserved ejection fraction. Chin Med J (Engl). 2020 Feb 5;133(3):364-6. https://doi.

org/10.1097/CM9.0000000000000631
35. Mfeukeu-Kuate L, Yemele HK, Jingi AM, Etoa M, Nkeck JR, Boombhi J, et al. Burden, Type, and Associated Factors of Thyroid Dysfunction in Patients with Heart Failure in Sub-Saharan Africa: A Cross-Sectional Study. World J Cardiovasc Dis. 2021;11:485-97. https://doi.org/10.4236/wjcd.2021.1111046
36. Mohamud MA, İbrahim İG, Ahmed SA, Karataş M, Jeele MOO. Prevalence of Thyroid Dysfunction Among Patients with Heart Failure at a Tertiary Hospital in Mogadishu, Somalia. Int J Gen Med. 2022 Jul 28;15:6335-9. https://doi.org/10.2147/ijgm.s371697
37. Salzano A, Marra AM, Ferrara F, Arcopinto M, Bobbio E, Valente P, et al. Multiple hormone deficiency syndrome in heart failure with preserved ejection fraction. Int J Cardiol. 2016 Dec 15;225:1-3. https://doi.org/10.1016/j.ijcard.2016.09.085
38. Sato Y, Yoshihisa A, Kimishima Y, Kiko T, Kanno Y, Yokokawa T, et al. Low T3 Syndrome Is Associated With High Mortality in Hospitalized Patients With Heart Failure. J Card Fail. 2019 Mar;25(3):195-203. https://doi.org/10.1016/j.cardfail.2019.01.007
39. Rywik TM, Doryńska A, Wiśniewska A, Cegłowska U, Drohomirecka A, Topór-Mądry R, et al. Epidemiology and clinical characteristics of hospitalized patients with heart failure with reduced, mildly reduced, and preserved ejection fraction. Pol Arch Intern Med. 2022 May 30;132(5):16227. https://doi.org/10.20452/pamw.16227
40. Amanai S, Harada T, Kagami K, Yoshida K, Kato T, Wada N, et al. The H_2FPEF and HFA-PEFF algorithms for predicting exercise intolerance and abnormal hemodynamics in heart failure with preserved ejection fraction. Sci Rep. 2022 Jan 7;12(1):13. https://doi.org/10.1038/s41598-021-03974-6
41. Sun Y, Wang N, Li X, Zhang Y, Yang J, Tse G, et al. Predictive value of H2FPEF score in patients with heart failure with preserved ejection fraction. ESC Heart Fail. 2021;8:1244-52. https://doi.org/10.1002/ehf2.13187
42. Tao Y, Wang W, Zhu J, You T, Li Y, Zhou X. H2FPEF score predicts 1-year rehospitalisation of patients with heart failure with preserved ejection fraction. Postgrad Med J. 2021 Mar;97(1145):164-7. https://doi.org/10.1136/postgradmedj-2019-137434
43. Flamant F, Gauthier K. Thyroid hormone receptors: the challenge of elucidating isotype-specific functions and cell-specific response. Biochim Biophys Acta. 2013 Jul;1830(7):3900-7. https://doi.org/10.1016/j.bbagen.2012.06.003
44. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012 Sep;122(9):3035-43. https://doi.org/10.1172/jci60047
45. von Hafe M, Neves JS, Vale C, Borges-Canha M, Leite-Moreira A. The impact of thyroid hormone dysfunction on ischemic heart disease. Endocr Connect. 2019 May 1;8(5):R76-90. https://doi.org/10.1530/ec-19-0096
46. Marín-García J. Thyroid hormone and myocardial mitochondrial biogenesis. Vascul Pharmacol. 2010 Mar-Apr;52(3-4):120-30. https://doi.org/10.1016/j.vph.2009.10.008
47. Berta E, Lengyel I, Halmi S, Zrínyi M, Erdei A, Harangi M, et al. Hypertension in Thyroid Disorders. Front Endocrinol (Lausanne). 2019 Jul 17;10:482. https://doi.org/10.3389/fendo.2019.00482
48. Marvisi M, Balzarini L, Mancini C, Mouzakiti P. Thyroid gland and pulmonary hypertension. What's the link? Panminerva Med. 2013 Mar;55(1):93-7.
49. Kositanurit W, Kittipibul V, Srichomkwun P, Boonyaratavej S, Puwanant S. Clinical phenotypes and prognosis of thyrotoxic heart failure and cardiomyopathy in patients hospitalized for acute heart failure. ESC Heart Fail. 2021 Aug;8(4):2776-83. https://doi.org/10.1002/ehf2.13347
50. Shojaeifard M, Davoudi Z, Erfanifar A, Fattahi Neisiani H, Erami S, Bakhshandeh H, et al. Evaluation of diastolic function in newly diagnosed hyperthyroid patients with preserved left ventricular systolic function. Cardiovasc Endocrinol Metab. 2020 Nov 19;10(3):186-90. https://doi.org/10.1097/xce.0000000000000238
51. Goldman S, McCarren M, Morkin E, Ladenson PW, Edson R, Warren S, et al. DITPA (3,5-Diiodothyropropionic Acid), a thyroid hormone analog to treat heart failure: phase II trial veterans affairs cooperative study. Circulation. 2009 Jun 23;119(24):3093-100. https://doi.org/10.1161/circulationaha.108.834424