ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2776–2783
Published online 1 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13347

ORIGINAL RESEARCH ARTICLE

Clinical phenotypes and prognosis of thyrotoxic heart failure and cardiomyopathy in patients hospitalized for acute heart failure

Weerapat Kositanurit[1,2,3], Veraprapas Kittipibul[1,2], Panudda Srichomkwun[2,4,5], Smonporn Boonyaratavej[1,2] and Sarinya Puwanant[1,2]*

[1]*Division of Cardiovascular Medicine, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bhumisiri Mangkhalanusorn Building, M Floor, Zone C, 1873 Rama IV Rd, Bangkok, Pathumwan 10330, Thailand;* [2]*Cardiac Center, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand;* [3]*Department of Physiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; and* [4]*Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;* [5]*Excellent Center in Diabetes, Hormones and Metabolism, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand*

Abstract

Background We sought to examine clinical characteristics and outcomes in patients hospitalized for acute heart failure (HF) and thyrotoxicosis.

Methods Patients with thyrotoxic HF were compared with age and gender-matched patients hospitalized for acute HF (controls). Thyr-HF was defined by the Framingham criteria for HF and clinical hyperthyroidism. Thyrotoxic cardiomyopathy was defined as left ventricular ejection fraction (LVEF) $<$ 55%.

Results Of 11 109 consecutive patients hospitalized for acute HF between 1 January 2002 and 1 January 2017, 92 patients (0.8%) had thyrotoxic HF. Clinical and echocardiographic data were available in 87 patients (age 51 ± 16 years; 74% female), representing the study population. Compared with controls, patients with Thyr-HF had a smaller body surface area (BSA), a higher LVEF, a lower LV end-diastolic diameter, a higher tricuspid annular plane systolic excursion (TAPSE), higher blood pressure, higher heart rate, and were more likely to have right-sided HF at presentation ($P < 0.01$ for all). The survival rate among patients with thyrotoxic HF was higher than the control group (HR: 4.3; 95% CI: 2.1–9.5). Fifty-eight percent of patients with thyrotoxic HF had thyrotoxic cardiomyopathy. In multivariate analysis, TAPSE (OR = 46; 95% CI: 1.04–2008.20; $P = 0.047$) and leukocytosis (OR = 16; 95% CI 1.01–259.39; $P = 0.049$) correlated with thyrotoxic cardiomyopathy. LV recovery was observed in 69% of these patients.

Conclusions Thyrotoxic HF was uncommon among patients hospitalized for acute HF. However, after definitive therapy, these patients had a more favourable prognosis than those hospitalized for acute HF without thyrotoxic HF. Clinical phenotypes of thyrotoxic HF include small BSA, middle-aged female, HF-pEF, and right-sided HF. Thyrotoxic cardiomyopathy affected over half of the patients with thyrotoxic HF with a two-third recovery rate.

Keywords Acute heart failure; Outcome; Thyrotoxicosis; Cardiomyopathy; Thyroid

Received: 4 December 2020; Revised: 20 March 2021; Accepted: 25 March 2021
**Correspondence to: Sarinya Puwanant, Division of Cardiovascular Medicine, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bhumisiri Mangkhalanusorn Building, M Floor, Zone C, 1873 Rama IV Rd, Pathumwan, Bangkok 10330, Thailand. Tel: +66-83656651. Email spuwanant@gmail.com*

Introduction

Thyroid hormones regulate key cardiac genes and effects on myocyte and systemic vasculature altering cardiovascular haemodynamics, including tachycardia, increased myocardial contractility/ejection fraction (EF), increased cardiac output, increased blood volume, and lower systemic vascular resistance (SVR).[1–4] A recent study found that high-output heart failure (HF) was associated with increased mortality; however, patients with HF and thyrotoxicosis were excluded from the study.[5] Thyroid disorders are common problems in patients with HF.[6,7] Thyrotoxicosis or hyperthyroidism complicated

with acute HF has been previously described in case reports.[8–12] However, there is a paucity on systematic data of clinical phenotypes and prognosis of patients hospitalized for acute HF and thyrotoxicosis. Furthermore, little is known about the effects of the excess circulating thyroid hormones on left and right ventricular (RV) function and pulmonary pressure in those patients. Therefore, we examined the prevalence, clinical and echocardiographic characteristics, and clinical outcomes of patients hospitalized for acute HF with thyrotoxicosis.

Methods

Patients and definitions

Between 1 January 2002 and 1 January 2017, consecutive patients hospitalized for acute HF and thyrotoxicosis were identified. The study population includes patients hospitalized with a diagnosis of HF (International Classification of Disease-10th [ICD-10] I 500–504, I 508–509), who met the Framingham criteria for HF and a diagnosis of thyrotoxicosis (ICD-10 E05).[13] Thyrotoxic HF was defined by the Framingham criteria for the diagnosis of HF coupled with the presence of a clinical syndrome characterized by hyper-metabolism and hyperactivity due to excess circulating free thyroid hormones,[3,13,14] including serum-free thyroxine (FT4) $>$ 1.8 ng/dL, free triiodothyronine (FT3) $>$ 4 pg/mL, and serum thyroid-stimulating hormone (TSH) level $<$ 0.3 μIU/mL. Thyroid hormones were measured by electrochemiluminescence immunoassay on a Cobas analyser (Roche Diagnostics, Thailand).[15] Those cut-off values for thyroid hormones were based on an internal validation of a previous cohort in the Thai population.[15,16] Graves' disease was diagnosed based on the clinical presentation of diffuse goitre and biochemical tests consisting of primary hyperthyroidism.[17] Thyroid storm was diagnosed by the Burch and Warsofsky's score of 45 or greater.[18–20] Patients with thyrotoxic HF were compared with age and gender-matched patients hospitalized for acute HF in the corresponding periods (controls) in a 1:1 ratio. Clinical and echocardiographic data were taken from medical records review and reanalysis of echocardiographic data in the Echo PAC system. A transthoracic echocardiogram was performed in hospitalized patients using commercially available ultrasound machines, Vivid 7 GE-Vingmed (Milwaukee, WI), and IE-33 Philips (Philips Medical System, Andover, MA). The echocardiographic images were digitally stored in the EchoPAC and QLAB software packages for off-line analysis. Right-sided HF was determined by the presence of one of the following signs of HF resulting from RV dysfunction: elevated jugular venous pulse (JVP), lower extremity oedema, or positive hepatojugular reflux.[21] Thyrotoxic cardiomyopathy was defined as left ventricular ejection fraction (LVEF) $<$ 55% and the clinical syndrome of thyrotoxicosis.[22,23] Recovery of thyrotoxic cardiomyopathy was defined as LVEF $\geq$ 55%, with an improvement of LVEF of 15% or greater. Heart failure with reduced EF (HF-rEF), mid-range EF (HF-mEF), and preserved EF (HF-pEF) were defined according to the ESC guidelines for acute and chronic HF.[24] Pulmonary hypertension (PH) was defined as peak pulmonary systolic pressures (PASP) $>$ 35 mmHg estimated by Doppler echocardiography.[25,26] The study protocol was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No. 253/61).

Clinical outcomes

Overall mortality was determined by medical records, death certificates, or telephone interviews. Five (6%) and two (2%) patients were lost to follow-up in the thyrotoxic HF group and control group, respectively.

Statistical analysis

Descriptive data were presented by frequency, percentage, median, and mean ± standard deviation (SD). Differences in continuous variables were determined by a student's t-test or a Wilcoxon–rank-sum test. Categorical variables were compared using a χ^2 test or a Fisher's exact test. To identify the predictors of thyrotoxic cardiomyopathy, univariate analysis was performed comparing the presence of thyrotoxic cardiomyopathy with demographic, clinical, and echocardiographic characteristics. Multivariate analysis was performed to identify if the addition of variables improved the prediction of thyrotoxic cardiomyopathy. The first model included age and gender followed by the addition of each variable with a *P*-value of $\leq$0.1 based on the univariate analysis. Kaplan–Meier curves were plotted to estimate survival between groups, based on the log-rank test. *P* values $<$0.05 were considered statistically significant. Statistical analyses were conducted using Stata version 16 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics and clinical phenotypes of thyrotoxic HF

Of 11 109 consecutive patients hospitalized for acute HF between 1 January 2002 and 1 January 2017, 92 patients (1%) had thyrotoxic HF. Clinical and echocardiographic data were available in 87 patients, representing the study population. Of study patients (age, 51 ± 16 years; 74% female) with thyrotoxic HF, 84%, 52%, and 24% had Graves' disease, thyroid storm, and HF-rEF, respectively. Eighty patients (93%)

presented with clinical right-sided HF, including elevated JVP in 65 patients (74%), positive hepatojugular reflux in seven patients (8%), and bilateral pitting oedema of lower extremities in 63 patients (72%). Mean serum FT3, serum FT4, and serum TSH was 12.6 pg/mL, 5.0 ng/dL, and 0.01 μIU/mL, respectively. The median duration of symptoms before HF admission was 10 (1–365) days. Thyrotoxicosis was treated with antithyroid drugs in all patients, radionuclide iodine (I^{131}) therapy in 55%, and surgical thyroidectomy in 3%. *Table 1* shows baseline characteristics in patients with thyrotoxic HF and controls. Compared with controls, patients hospitalized for thyrotoxic HF had smaller body surface area (BSA), smaller body mass index (BMI), higher blood pressure, higher heart rate, higher LVEF, lower LV end-diastolic diameter, higher PASP, higher tricuspid annular plane systolic excursion (TAPSE), lower serum creatinine, and were more likely to have PH and right-sided HF at presentation ($P < 0.01$ for all).

Thyrotoxic cardiomyopathy

Of the 87 patients with thyrotoxic HF, 50 patients (58%) had thyrotoxic cardiomyopathy. *Table 2* shows the clinical and echocardiographic characteristics of study patients with and without thyrotoxic cardiomyopathy. Serum thyroid hormones, heart rate, atrial fibrillation, age, or gender were not different between patients with and without thyrotoxic cardiomyopathy, while greater white blood counts (8429 vs. 6598 cells/mL, $P = 0.002$), greater proportion of propylthiouracil (PTU) use as an antithyroid drug (44% vs. 20%, P = 0.024), greater dilated LV end-diastolic diameter (57 vs. 48 mm, $P < 0.001$), and lower TAPSE (15 vs. 21 mm, $P = 0.0004$) were observed in patients with thyrotoxic cardiomyopathy compared with those without thyrotoxic cardiomyopathy. In multivariate analysis, TAPSE (OR = 46, 95% CI: 1.01–259.39, $P = 0.04$) and leukocytosis (OR = 16, 95% CI: 1.04–2008.20, $P = 0.049$) were associated with thyrotoxic cardiomyopathy in patients hospitalized for thyrotoxic HF (*Table 3*). Among patients with thyrotoxic cardiomyopathy, 32 (64%) had a complete follow-up echocardiographic study for analysis. Over the mean follow-up period of 18 months, 22 patients (69%) had recovery of LV systolic function. Heart rate, atrial fibrillation, thyroid hormone levels, or TSH levels were not different between patients with and without LV recovery at the follow-up periods.

Clinical outcomes

During the 5-year follow-up period, nine patients (10%) with thyrotoxic HF and 47 controls (54%) died. One patient (1%) with thyrotoxic HF died in-hospital from ventricular

Table 1 Baseline characteristics

Parameters	Thyrotoxic heart failure requiring hospitalization ($n = 87$)	Acute heart failure requiring hospitalization ($n = 87$)	*P* value
Age (years)	51 ± 16	49 ± 15	0.794
Sex (female)	64 (74%)	61 (70%)	0.613
Body surface area (m^2)	1.56 ± 0.19	1.69 ± 0.24	<0.001*
Body mass index (kg/m^2)	22.5 ± 4.7	23.9 ± 5.0	0.040*
Clinical features			
Right heart failure (*n*, %)	84 (97%)	60 (69%)	<0.001*
Systolic blood pressure (mmHg)	133 ± 27	117 ± 19	<0.001*
Heart rate (b.p.m.)	109 ± 34	82 ± 16	<0.001*
Atrial fibrillation (*n*, %)	32 (37%)	35 (40%)	0.427
Laboratories			
Creatinine (mg/dL)	0.71 ± 0.43	1.27 ± 0.73	<0.001*
White blood cells ($cells/mm^3$)	7718 ± 3239	7488 ± 3864	0.805
Potassium (mEq/L)	3.9 ± 0.7	4.1 ± 0.6	0.125
NT-pro BNP (pg/mL)	4062 ± 3556	8760 ± 1071	0.588
Echocardiography			
LVEDD (mm)	53 ± 8	56 ± 10	0.006*
LVEF (%)	51 ± 17	38 ± 24	<0.001*
TAPSE (mm)	18 ± 5	14 ± 4	0.009*
PASP (mmHg)	48 ± 15	43 ± 14	0.008*
PASP > 35 mmHg	52/60[a] (87%)	50/72[b] (69%)	0.002*
HF phenotype (*n*, %)			
HF-rEF	21 (24%)	56 (64%)	<0.001*
HF-mEF	15 (17%)	2 (2%)	
HF-pEF	51 (59%)	29 (33%)	

Data are presented as mean ± SD or count (percentage).
*Statistical significance ($P < 0.05$).
[a]Of 87 patients, 60 patients had a complete spectral Doppler of tricuspid regurgitation for analysis.
[b]Of 87 patients, 72 patients had a complete spectral Doppler of tricuspid regurgitation for analysis.
EF, ejection fraction; HF, heart failure; HF-mEF, heart failure with mid-range ejection fraction; HF-pEF, heart failure with preserved EF; HF-rEF, heart failure with reduced EF; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular EF; NT-pro BNP, N-terminal pro b-type natriuretic peptide; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

DOI: 10.1002/ehf2.13347

Table 2 Clinical and echocardiographic characteristics of patients hospitalized for thyrotoxic HF with and without thyrotoxic cardiomyopathy

Parameters	Thyrotoxic cardiomyopathy		*P* value
	Present (n = 50)	Absent (n = 37)	
Age (years)	49 ± 17	53 ± 14	0.283
Female (n, %)	35 (70%)	29 (78%)	0.613
Clinical features			
Thyroid storm (n, %)	26 (52%)	20 (54%)	0.850
Right heart failure (n, %)	45 (92%)	35 (95%)	0.619
Systolic blood pressure (mmHg)	132 ± 29	135 ± 24	0.332
Heart rate (b.p.m.)	114 ± 34	102 ± 34	0.126
Atrial fibrillation (n, %)	17 (34%)	15 (41%)	0.537
Treatment (n, %)			
Antithyroid drugs	50 (100%)	37 (100%)	0.291
Iodine^{131} therapy	24 (48%)	24 (64%)	
Surgery	2 (4%)	1 (3%)	
PTU: methimazole	29: 21 (58:42%)	29: 8 (78:22%)	0.046*
Beta-blocker	20 (40%)	14 (39%)	0.833
ACE-I/ARB	22 (44%)	11 (30%)	0.175
MRA	3 (5%)	0	0.520
Digoxin	24 (48%)	11 (30%)	0.009
Diuretics	47 (94%)	31 (83%)	0.714
Laboratories			
FT3 (pg/mL)	12 ± 8	14 ± 9	0.476
FT4 (ng/dL)	4.9 ± 2.1	5.0 ± 2.3	0.795
TSH (μIU/mL)	0.012 ± 0.032	0.009 ± 0.010	0.144
Creatinine (mg/dL)	0.78 ± 0.48	0.61 ± 0.32	0.075
White blood cells (cells/mm^3)	8429 ± 3297	6598 ± 3278	0.002*
Potassium (mEq/L)	4.0 ± 0.8	3.8 ± 0.5	0.349
Echocardiography			
LVEDD (mm)	57 ± 8	48 ± 5	<0.001*
LVEF (%)	40 ± 13	66 ± 7	<0.001*
TAPSE (mm)	15 ± 5	21 ± 3	0.0004*
PASP (mmHg)	46 ± 12	49 ± 18	0.146
PASP > 35 mmHg	27/32[a] (84%)	25/28[a] (89%)	0.576
HF phenotype (n, %)			
HF-rEF	22 (44%)	0	<0.001*
HF-mEF	14 (28%)	0	
HF-pEF	14 (28%)	37 (100%)	

Data are presented as mean ± SD or count (percentage).
*Statistical significance ($P < 0.05$).
[a]Patients had a complete spectral Doppler of tricuspid regurgitation for analysis.
ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; EF, ejection fraction; FT3, free triiodothyronine; FT4, free thyroxine; HF, heart failure; HF-mEF, heart failure with mid-range ejection fraction; HF-pEF, heart failure with preserved EF; HF-rEF, heart failure with reduced; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular EF; MRA, mineralocorticoid receptor antagonists; NT-pro BNP, N-terminal pro b-type natriuretic peptide; PASP, pulmonary artery systolic pressure; PTU, propylthiouracil; TAPSE, tricuspid annular plane systolic excursion; TSH, thyroid stimulating hormone.

arrhythmia and multiorgan failure. The rate of survival among survivors of in-hospital death in patients with thyrotoxic HF was higher than that in controls (hazard ratio: 4.3; 95% CI: 2.1–9.5; $P < 0.001$) (*Figure 1A*). There was no difference in survival between thyrotoxic HF patients with and without cardiomyopathy (hazard ratio: 1.2; 95% CI: 0.3–3.6; $P = 0.967$) (*Figure 1B*).

Discussion

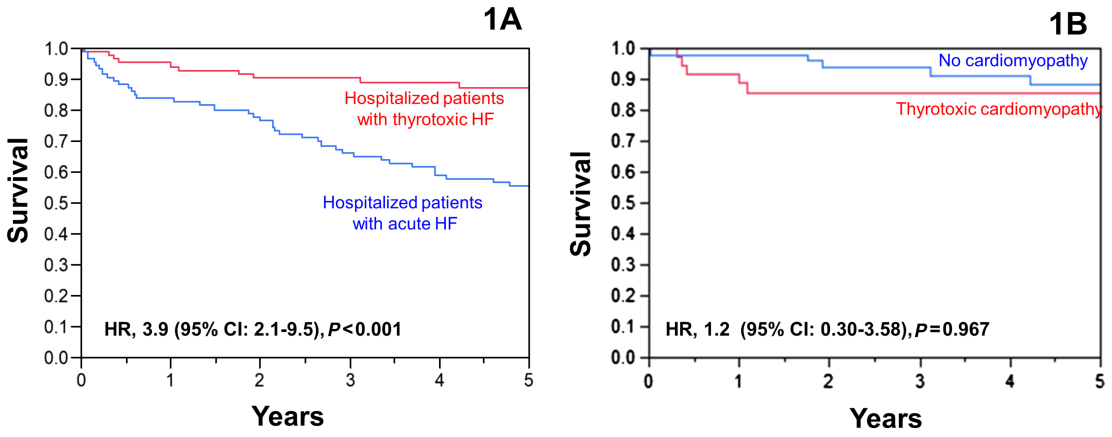
The major findings of our study are (i) the prevalence of thyrotoxic HF in patients hospitalized for acute HF was uncommon, only 1%; (ii) the most common cause of thyrotoxic HF in hospitalized patients was Graves' disease, accounting for 84%; (iii) key clinical features of thyrotoxic HF included small middle-aged female, right-sided HF, tachycardia, and HF-preserved EF; (iv) thyroid storm was found in approximately half of the patients hospitalized for thyrotoxic HF; (v) thyrotoxic cardiomyopathy was present in half of the hospitalized patients with thyrotoxic HF with a 69% chance of recovery after definitive treatment; and (vi) In-hospital mortality of overall thyrotoxic HF was 1%; however, patients with thyrotoxic HF who received definitive treatment had a more favourable prognosis compared with general patients hospitalized for acute HF.

Table 3 Predictors of thyrotoxic cardiomyopathy

	Univariate			Multivariate		
Variables	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age <60 years	3.44	1.22–9.76	0.02	2.22	0.24–20.18	0.480
Female	0.64	0.24–1.73	0.61	3.99	0.24–66.86	0.340
Clinical features						
Thyroid storm	0.92	0.39–2.16	0.85			
Right heart failure	0.64	0.11–3.71	0.62			
Atrial fibrillation	0.76	0.31–1.82	0.53			
Treatment						
Iodine^{131} therapy	1	0.08–12.16	1.00			
Surgery	0.50	0.20–1.22	0.13			
PTU: methimazole	0.38	0.15–1.00	0.05	2.34	0.24–23.06	0.470
Beta-blocker	1.10	0.46–2.62	0.84			
ACE-I/ARB	1.86	0.76–4.56	0.18			
Laboratories						
FT3 ≥ 9 pg/mL	0.54	0.23–1.30	0.17			
FT4 ≥ 8 ng/dL	0.88	0.32–2.40	0.80			
White blood cells >6300 cells/mm^3	5.69	2.18–14.88	<0.01	16.21	1.01–259.39	0.049
Potassium ≤4 mEq/L	0.52	0.21–1.28	0.16			
Echocardiography						
TAPSE <18 mm	11.25	1.17–108.41	0.036	45.8	1.04–2008.2	0.047
PASP >35 mmHg	0.65	0.14–3.00	0.58			

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; FT3, free triiodothyronine; FT4, free thyroxine; LVEDD, left ventricular end-diastolic diameter; PASP, pulmonary artery systolic pressure; PTU, propylthiouracil; TAPSE, tricuspid annular plane systolic excursion.

Figure 1 (A) Kaplan–Meier survival curves for patients hospitalized for thyrotoxic HF and hospitalized patients with general acute HF. (B) Kaplan–Meier survival curves for thyrotoxic heart failure patients with and without thyrotoxic cardiomyopathy.



Prevalence and clinical phenotype of thyrotoxic HF

We demonstrated that thyrotoxic HF was uncommon (1%) among patients hospitalized for acute HF. The prevalence of thyrotoxic HF in patients with acute HF was less than that reported in the chronic HF population. Previous studies[27,28] observed that clinical hyperthyroidism was found in about 6–19% of outpatient patients with HF. The prevalence of thyrotoxic HF in patients hospitalized for acute HF has not been described. We found that up to 90% of patients hospitalized for thyrotoxic HF presented with right-sided HF. These findings were consistent with previous case reports demonstrating that right-sided HF was common in thyrotoxicosis.[11,12] Paran *et al*. and Thurnheer *et al*. suggested that PH was the major mechanism linked to right-sidedHF in thyrotoxicosis.[12,29] Marvasi *et al*. reported that 65% of ambulatory patients with hyperthyroidism caused by Graves' disease had PH.[30] In the present study, the mean PASP estimated by echocardiogram was 48 mmHg, which was higher than that observed in patients hospitalized for acute HF. Furthermore, we found that 87% of patients

DOI: 10.1002/ehf2.13347

with thyrotoxic HF had PH. The greater prevalence of PH in our study was likely explained by the larger number of critically ill patients compared with those studied in the ambulatory HF setting. The common phenotypes of thyrotoxic HF were small middle-aged females with normal EF. These phenotypes stand in contrast to those described in classic HF-pEF, typically older women with high BMI and BSA.[5,31] Patients with thyrotoxic HF had a higher heart rate and higher blood pressure than controls.[32] The effects of the T3 hormone on cardiovascular haemodynamics have been well described in previous literature.[1,2,33] Thyroid hormone increases basal metabolism in almost all tissue and organ systems, leading to an increase in preload, myocardial contractility, and cardiac output.[1] Additionally, the genomic effects of the T3 hormone regulate the beta-1 adrenergic receptor and affect the action potential in cardiac pacemaker through accelerated diastolic depolarization secondary to an increase in cyclic adenosine monophosphate (cAMP).[1,2] In our study, 37% of patients had atrial fibrillation. The prevalence of atrial fibrillation in patients with hyperthyroidism has been shown to range from 2% to 39%.[1,23] It is unclear as to how the thyroid hormone predisposes to atrial fibrillation.[2] Notably, about half of the patients hospitalized for thyrotoxic HF had thyroid storm at presentation. This proportion was considerably higher than previously reported. A study in Japan showed that 5.4% of patients hospitalized for thyrotoxicosis had thyroid storm.[18] The possible explanation of the high proportion of thyroid storm in our study may be that the study population consisted of patients hospitalized for acute HF, representing a sicker patient population and underscreening before the presentation.

Thyrotoxic cardiomyopathy and heart failure with recovered ejection fraction

Previous studies have described LV dysfunction among outpatients with hyperthyroidism and chronic HF.[23,32] However, there are limited data on the prevalence of thyrotoxic cardiomyopathy in patients hospitalized for acute HF. We demonstrated that 58% of hospitalized patients with thyrotoxic HF had cardiomyopathy. This prevalence rate was higher than previously reported in ambulatory patients with hyperthyroid.[23,32] Siu *et al*. studied the clinical characteristics of 34 patients with primary hyperthyroidism presenting with HF in a thyroid clinic.[32] About half of their patients with thyrotoxic HF had Graves' disease. They found that 47% had LV systolic dysfunction.[32] A more recent study by Oliveros-Ruiz *et al*. examined the recovery of thyrotoxic cardiomyopathy in ambulatory patients with hyperthyroidism.[23] Although they did not include HF syndrome in the inclusion criteria, the authors showed that 37% of patients with hyperthyroidism had persistent LV dysfunction on 6 months follow-up. Siu *et al*. demonstrated that 31% of patients with HF and hyperthyroidism had persistent LV dysfunction at 12 month follow-up.[32] Similarly, we found that 31% of patients hospitalized for thyrotoxic HF had persistent cardiomyopathy at 18 months. The possible pathomechanisms of thyrotoxic cardiomyopathy include tachycardia-induced cardiomyopathy, direct myopathic effect caused by T3 hormone, and concomitant auto-immune myocarditis associated with Graves' disease.[1,2,4,33] However, heart rate and thyroid hormone levels in patients with and without LV recovery were not different in this study. These findings were consistent with those reported by Siu *et al*.[32] Therefore, the key mechanism of thyrotoxic cardiomyopathy remains elusive. Interestingly, we found that lower TAPSE was associated with thyrotoxic cardiomyopathy, suggesting that RV dysfunction was concordant with the degree of LV systolic dysfunction in the setting of acute thyrotoxic HF. Furthermore, we demonstrated that leukocytosis was another independent factor associated with thyrotoxic cardiomyopathy. It is likely that leukocytosis is attributed to the stress response from the critical hyperthyroid state or concomitant myocarditis. Incorporating cardiac magnetic resonance data could further define this aspect.

Prognosis of patients hospitalized for acute thyrotoxic heart failure

One patient with HF and thyroid storm died in the hospital because of refractory ventricular arrhythmia and multiorgan failure. This equates to an in-hospital mortality of 1% and 2% among patients hospitalized with thyrotoxic HF and thyroid storm, respectively. The in-hospital mortality rate of thyroid storm in this study was lower than those reported by previous studies.[18,34] Akamizu *et al*. suggested that the overall mortality rate of thyroid storm was 10%.[18,19] In our cohort, patients with thyrotoxic HF who were survivors from in-hospital deaths had a more favourable prognosis than general patients hospitalized with acute HF. Recently, Yogesh *et al*. demonstrated increased mortality in high-output HF.[5] However, they excluded patients with thyrotoxicosis and anaemia from the study population. Our findings highlight that not every high-output HF carried a poor prognosis. Thyrotoxic HF had a favourable prognosis if the definitive treatment was timely commenced. The recovery and reversibility of LV systolic function may play a pivotal role in determining prognosis in this entity of HF.

Study limitations

First, the care of thyroidal disease in the present study was conducted in a tertiary care academic centre setting where the I^{131} ablative therapy is preferable, which could limit the applicability and generalizability of our findings. Second, data of treatment and echocardiogram after hospital discharge

were not available for every patient. Third, the causes of death were not available. Fourth, PH was mainly defined by echocardiographic estimation of pulmonary artery systolic pressure, instead of right heart catheterization. Lastly, this study is limited by its retrospective nature. We recommend a multi-centre cohort with a larger number of patients to clarify and expand these initial findings.

Conclusions

Thyrotoxic HF was uncommon among patients hospitalized for acute HF. However, after definitive treatment for hyperthyroidism and HF, these patients had a more favourable prognosis than general patients hospitalized for acute HF. Thyrotoxic cardiomyopathy was present in half of the hospitalized patients with thyrotoxic HF with a two-thirds rate of treatment recovery. Thyrotoxic HF should be considered in the differential diagnosis in patients presenting with clinical phenotypes of small middle-aged females with HF-pEF and the clinical syndrome of right-sided HF, tachycardia, and relatively hypertensive manifestation.

Acknowledgements

We thank Paisit Kosum, MD, for his assistance in providing data from the acute heart failure cohort (control group) and Michael D. Ullman, Ph.D., for editing a draft of the manuscript.

Conflict of interest

None declared.

Funding

This research was supported by the Ratchadapisek Sompoch Endowment Fund (2018), Chulalongkorn University (grant no. RA 61/117).

References

1. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007; **116**: 1725–1735.
2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001; **344**: 501–509.
3. Dahl P, Danzi S, Klein I. Thyrotoxic cardiac disease. *Curr Heart Fail Rep* 2008; **5**: 170–176.
4. Khan R, Sikanderkhel S, Gui J, Adeniyi AR, O'Dell K, Erickson M, Malpartida J, Mufti Z, Khan T, Mufti H, Al-Adwan SA. Thyroid and Cardiovascular Disease: A Focused Review on the Impact of Hyperthyroidism in Heart Failure. *Cardiol Res* 2020; **11**: 68–75.
5. Reddy YNV, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-Output Heart Failure: A 15-Year Experience. *J Am Coll Cardiol* 2016; **68**: 473–482.
6. Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, Cappola TP, Cappola AR. Thyroid Dysfunction in Heart Failure and Cardiovascular Outcomes. *Circ Heart Fail* 2018; **11**: e005266.
7. Danzi S, Klein I. Thyroid abnormalities in heart failure. *Heart Fail Clin* 2020; **16**: 1–9.
8. Choudhury RP, MacDermot J. Heart failure in thyrotoxicosis, an approach to management. *Br J Clin Pharmacol* 1998; **46**: 421–424.
9. Goland S, Shimoni S, Kracoff O. Dilated cardiomyopathy in thyrotoxicosis. *Heart* 1999; **81**: 444–445.
10. Cavros NG, Old WD, Castro FD, Estep HL. Case report: reversible mitral regurgitation and congestive heart failure complicating thyrotoxicosis. *Am J Med Sci* 1996; **311**: 142–144.
11. Park JH, Shong M, Lee JH, Choi SW, Jeong JO, Seong IW. Reversible severe tricuspid regurgitation with right heart failure associated with thyrotoxicosis. *Thyroid* 2006; **16**: 813–814.
12. Paran Y, Nimrod A, Goldin Y, Justo D. Pulmonary hypertension and predominant right heart failure in thyrotoxicosis. *Resuscitation* 2006; **69**: 339–341.
13. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971; **285**: 1441–1446.
14. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet* 2016; **388**: 906–918.
15. Center for Medical Diagnostic Laboratories Faculty of Medicine Chulalongkorn University. *Manual of Diagnostic Laboratories*. Bangkok: King Chulalongkorn Memorial Hospital; 2020.
16. Sriphrapradang C, Pavarangkoon S, Jongjaroenprasert W, Chailurkit LO, Ongphiphadhanakul B, Aekplakorn W. Reference ranges of serum TSH, FT4 and thyroid autoantibodies in the Thai population: the national health examination survey. *Clin Endocrinol (Oxf)* 2014; **80**: 751–756.
17. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid* 2016; **26**: 1343–1421.
18. Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Monden T, Kouki T, Otani H, Teramukai S, Uehara R, Nakamura Y, Nagai M, Mori M, Japan Thyroid Association. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid* 2012; **22**: 661–679.
19. Akamizu T. Thyroid storm: a Japanese perspective. *TThyroid* 2018; **28**: 32–40.
20. Chiha M, Samarasinghe S, Kabaker AS. Thyroid storm: an updated review. *J Intensive Care Med* 2015; **30**: 131–140.
21. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FD, Raval AN, Ward C, American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the

American Heart Association. *Circulation* 2018; **137**: e578–e622.
22. Babenko AY, Bairamov AA, Grineva EN, Ulupova EO. Thyrotoxic Cardiomyopathy. In Veselka P. J., ed. *Cardiomyopathies - From Basic Research to Clinical Management Cardiomyopathies - From Basic Research to Clinical Management*. InTech; 2012.
23. Oliveros-Ruiz L, Vallejo M, Diez Canseco LF, Cárdenas M, Hermosillo JA. Determinants of thyrotoxic cardiomyopathy recovery. *Biomed Res Int* 2013; **2013**: 452709.
24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
25. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685–713 quiz 86-8.
26. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54**: S55–S66.
27. Sandler G, Wilson GM. The nature and prognosis of heart disease in thyrotoxicosis. A review of 150 patients treated with 131 I. *Q J Med* 1959; **28**: 347–369.
28. Summers VK, Surtees SJ. Thyrotoxicosis and Heart Disease. *Acta Med Scand* 1961; **169**: 661–671.
29. Thurnheer R, Jenni R, Russi EW, Greminger P, Speich R. Hyperthyroidism and pulmonary hypertension. *J Intern Med* 1997; **242**: 185–188.
30. Marvisi M, Zambrelli P, Brianti M, Civardi G, Lampugnani R, Delsignore R. Pulmonary hypertension is frequent in hyperthyroidism and normalizes after therapy. *Eur J Intern Med* 2006; **17**: 267–271.
31. Anand IS. High-output heart failure revisited. *J Am Coll Cardiol* 2016; **68**: 483–486.
32. Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. *Heart* 2007; **93**: 483–487.
33. Morkin E. Stimulation of cardiac myosin adenosine triphosphatase in thyrotoxicosis. *Circ Res* 1979; **44**: 1–7.
34. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin North Am* 2006; **35**: 663–686 vii.