Clinical features and long-term survival in idiopathic pulmonary arterial hypertension with thyroid dysfunction: insights from a national multicentre prospective study

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Shareable abstract (@ERSpublications)
IPAH patients with clinical hyper- or hypothyroidism have better haemodynamics and survival than IPAH without thyroid dysfunction, while those with subclinical hypothyroidism have similar profiles to those with euthyroid function https://bit.ly/3LUObZY

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Abstract

Background Our objective was to clarify the characteristics and long-term survival of idiopathic pulmonary arterial hypertension (IPAH) patients with thyroid dysfunction and compare them with IPAH without thyroid dysfunction.

Methods A retrospective analysis was conducted using prospectively collected data. IPAH patients with thyroid dysfunction at baseline were included. Patients with other subgroups of PAH and Group 2–5 pulmonary hypertension were excluded. IPAH patients with euthyroid function were matched 1:1 to IPAH patients with thyroid dysfunction by age and sex.

Results In total, 148 IPAH patients with thyroid dysfunction were included. Patients with hyperthyroidism, hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism accounted for 16.2%, 18.9%, 8.1% and 56.8%, respectively. IPAH patients with hyperthyroidism showed the highest mixed venous oxygen saturation (S_{vO_2}) and the lowest pulmonary vascular resistance (PVR) at baseline among subgroups, while patients with subclinical hypothyroidism had the lowest S_{vO_2} and highest PVR ($p<0.05$). Compared with IPAH without thyroid dysfunction, patients with hyperthyroidism (9.14 *versus* 13.86 WU; $p<0.05$) and hypothyroidism (10.70 *versus* 13.86 WU; $p<0.05$) showed significantly lower PVR. The haemodynamic profiles of patients with subclinical hypothyroidism were similar to IPAH with euthyroid function except for lower right atrial pressure (6 *versus* 8 mmHg; $p=0.009$). The long-term survival of patients with clinical thyroid dysfunction was better than IPAH without thyroid dysfunction, while that of those with subclinical diseases was comparable to the latter, even after adjusting for baseline haemodynamics and treatment.

Conclusion IPAH patients with clinical hyper- and hypothyroidism had better haemodynamics and survival than those without thyroid dysfunction, while patients with subclinical hypothyroidism had similar haemodynamics and survival profiles to the latter.

Introduction

Pulmonary arterial hypertension (PAH) can be associated with thyroid disease [1] and an increased prevalence of thyroid disease was observed in patients with PAH [2–4]. Thyroid function tests are recommended in all patients with PAH by the 2022 European Society of Cardiology/European Respiratory

Society guidelines for pulmonary hypertension (PH) [1], indicating that the association between thyroid disease and PAH is noteworthy and deserves further studies [5, 6].

Previous studies on thyroid disease in the PAH cohort mainly focused on the incidence of thyroid dysfunction in PAH patients and the correlation between thyroid hormones/autoantibodies and pulmonary haemodynamics [7–9]. Data on the clinical characteristics of PAH patients with thyroid dysfunction and the effect of thyroid function on outcomes of PAH were limited and inconsistent. The REVEAL registry reported that PAH patients with thyroid disease had demographic and haemodynamic profiles similar to those with none of the analysed comorbidities (including hypertension, obesity, type 2 diabetes, COPD, sleep apnoea, depression and thyroid disease) [10], while a small cohort of 58 patients with PAH revealed that patients with thyroid disease had longer PAH history and worse cardiac function than those with euthyroid function [11]. Notably, more than half of the patients in both of the two studies were PAH with associated conditions such as connective tissue disease and congenital heart disease [10, 11]. These associated conditions may influence the characteristics of patients, which can mask the impact of thyroid dysfunction in PAH. Excluding known associated conditions of PAH may reduce the confounding factors and can better explore the association between thyroid dysfunction and PAH. However, characteristics of patients with idiopathic PAH (IPAH) and thyroid dysfunction have not yet been reported.

Moreover, the study from the REVEAL registry found no significant differences in survival in PAH patients with and without thyroid disease [10]. However, an analysis from the Giessen PH Registry reported that thyroid-stimulating hormone (TSH) levels and free triiodothyronine (FT3) were prognostic factors in PAH [12]. Thus, further studies are warranted to explore the effect of thyroid function on outcomes of PAH. The long-term survival of IPAH patients with different levels of thyroid dysfunction remains to be investigated.

Therefore, based on the national multicentre prospective registry of PAH in China, we conducted a cohort study of IPAH patients with thyroid disease, to clarify the characteristics and long-term survival of IPAH patients with thyroid disease and compare them with those without thyroid dysfunction.

Methods

Study design and population

A cohort study of IPAH patients with thyroid dysfunction was conducted using data from the national multicentre prospective registry of PAH in China (ClinicalTrials.gov: NCT01417338), which was launched in August 2009 [13]. The study protocol was approved by the Institutional Review Board of Fuwai Hospital, Beijing, China (approval 2009-208).

The inclusion criteria for IPAH patients with thyroid dysfunction in this study were: 1) diagnosed as IPAH, defined by mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg, pulmonary arterial wedge pressure (PAWP) $\leqslant$15 mmHg and pulmonary vascular resistance (PVR) >3 WU on right heart catheterisation, and excluded other aetiologies of PAH and Group 2–5 PH; and 2) had thyroid disease, defined as an abnormal TSH level with or without an abnormal thyroxine level, or a history of thyroid disease on treatment. Detailed exclusion criteria are provided in the supplementary material.

Patients with IPAH and thyroid dysfunction were classified into clinical hyperthyroidism, clinical hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism groups according to their history of thyroid disease or the thyroid function at enrolment. For those with a history of thyroid disease, patients were assigned to the appropriate group based on their medical history regardless of their baseline thyroid function. IPAH patients with normal TSH, FT3 and free thyroxine (FT4) were matched 1:1 to those with thyroid dysfunction according to age and sex.

Baseline data were collected at enrolment. Patients were followed every 6 months *via* telephone calls, clinic visits or inpatient admission. The primary end-point was all-cause death. Details of data measurements, collection and follow-up are provided in the supplementary material.

Statistical analyses

Continuous variables are presented as mean±standard deviation or median (interquartile range (IQR)). Categorical data are presented as number (percentage). The characteristics of IPAH patients with hyperthyroidism, hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism were compared with matched IPAH patients with euthyroid function. For continuous data, two-group comparisons were made using the two-sample t-test or the Mann–Whitney U-test, according to the distribution; multigroup comparisons were made by one-way ANOVA and the Kruskal–Wallis test.

Categorical variables were compared by the Chi-squared test or Fisher's exact test, as appropriate. Survival analysis was performed using the Kaplan–Meier method and the differences were compared through the log-rank test. Baseline variables that were imbalanced at baseline among groups and were significantly associated with mortality were considered potential confounding factors. A Cox regression model was used to address potential confounding factors. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA) and R version 4.2.2 (www.r-project.org).

Results

Baseline characteristics of IPAH patients with and without thyroid dysfunction

In total, 148 IPAH patients with thyroid dysfunction were identified, including 24 (16.2%) patients with hyperthyroidism, 28 (18.9%) patients with hypothyroidism, 12 (8.1%) patients with subclinical hyperthyroidism and 84 (56.8%) patients with subclinical hypothyroidism. The baseline characteristics of these patients and matched IPAH without thyroid dysfunction are shown in table 1. The mean±SD age of IPAH patients with thyroid dysfunction at the time of PAH diagnosis was 34.3±10.8 years and 86.4% were female. A history of thyroid disease was reported by 62.5% and 64.3% of patients with hyper- and hypothyroidism, respectively, while few patients with subclinical thyroid dysfunction had a prior history of thyroid disease.

The haemodynamic profiles at baseline are shown in table 2. IPAH patients with hyperthyroidism showed the best haemodynamic profiles at baseline among subgroups, with the highest mixed venous oxygen saturation (S_{vO_2}) and the lowest total pulmonary resistance (TPR) and pulmonary vascular resistance (PVR), while patients with subclinical hypothyroidism had the lowest S_{vO_2} and highest TPR and PVR (p<0.05).

mPAP was comparable between IPAH patients with normal thyroid function and the subgroups of IPAH with thyroid dysfunction. However, PVR of patients with hyper- and hypothyroidism was 9.14 and 10.70 WU, respectively, both of which were significantly lower than IPAH without thyroid dysfunction (13.86 WU; all p<0.05). TPR of the two subgroups was also lower compared with IPAH with euthyroid function (median 10.29 and 12.50 WU, respectively, *versus* 15.95 WU; all p<0.05). In addition, IPAH with hyperthyroidism had higher S_{vO_2} (72.79±7.41% *versus* 66.18±9.47%; p=0.004) and cardiac index (CI) (median 2.95 *versus* 2.27 $L \cdot min^{-1} \cdot m^{-2}$; p=0.001) and lower right atrial pressure (RAP) (4.92±4.32 *versus* 8.99±6.73 mmHg; p=0.007) than those with normal thyroid function.

The haemodynamic profiles of IPAH patients with subclinical hypothyroidism were similar to those with normal thyroid function except for lower RAP (median 6 *versus* 8 mmHg; p=0.009). Nevertheless, these patients presented with higher N-terminal pro-brain natriuretic peptide (NT-proBNP) (median 760.7 *versus* 512.1 $pg \cdot mL^{-1}$) and higher levels of uric acid, total cholesterol and low-density lipoprotein (LDL) (table 1). Furthermore, forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and total lung capacity were significantly lower in patients with subclinical hypothyroidism than those with euthyroid function, although FEV_1/FVC was comparable between the two groups (table 1). Percentage predicted diffusing capacity of the lung for carbon monoxide (D_{LCO}) was also relatively lower in the former with borderline significance (59.25±16.28 *versus* 66.08±13.67; p=0.05).

Treatment

Considering treatment for thyroid disease, half of the patients with clinical hyperthyroidism received antithyroid drug therapy and 64.3% of the patients with hypothyroidism were on thyroid hormone therapy (table 3). PAH-targeted therapy was prescribed in 62.2% of patients with euthyroid function, and 75.0%, 92.9%, 83.3% and 87.6% of patients with hyperthyroidism, hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism, respectively. The majority of patients were on monotherapy. The combination rates of PAH-targeted therapy in patients with clinical and subclinical hypothyroidism were significantly higher than that in IPAH with euthyroid function (25.5% and 17.9%, respectively, *versus* 5.4%; all p<0.05) (table 3).

Long-term survival

During a median follow-up time of 5 years (maximum 11.3 years), 38 patients (25.6%) with thyroid dysfunction died. The estimated 1-, 3-, 5- and 10-year survival was 91.5%, 91.5%, 84.9% and 53.1%, respectively, for IPAH with hyperthyroidism; 100%, 96.2%, 91.6% and 83.3%, respectively, for IPAH with hypothyroidism; 91.7%, 71.4%, 71.4% and 71.4%, respectively, for IPAH with subclinical hyperthyroidism; and 95.2%, 84.5%, 69.2% and 41.6%, respectively, for IPAH with subclinical hypothyroidism. The 10-year survival of patients with clinical hyperthyroidism (53.1% *versus* 32.7%; p=0.05) and hypothyroidism

TABLE 1 Baseline characteristics of idiopathic pulmonary arterial hypertension (IPAH) patients with and without thyroid dysfunction

	IPAH without thyroid dysfunction	IPAH with thyroid dysfunction				p-value[#]
		Hyperthyroidism	Hypothyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism	
Subjects	148 (100)	24 (16.2)	28 (18.9)	12 (8.1)	84 (56.8)	
Age, years	34.2±11.2	32.6±11.8	39.6±10.0	35.1±11.8	32.9±11.1	0.042
Female	128 (86.5)	21 (87.5)	25 (89.3)	9 (75.0)	73 (86.9)	0.667
BMI, kg·m^{-2}	21.97±3.33	22.65±3.09	22.87±3.84	22.48±4.37	22.72±3.6	0.991
Time from symptom to PH diagnosis, months	8 (1.75–26)	10 (1–64)	5.5 (0.25–20.75)	1.5 (0–15.5)	10.5 (1–25)	0.221
Incident cases	128 (86.5)	19 (79.2)	23 (82.1)	11 (91.7)	63 (75.0)*	0.635
Thyroid dysfunction history	0	15 (62.5)*	18 (64.3)*	0	1 (1.2)	<0.001
WHO FC III–IV	69 (50.4)	14 (58.3)	17 (63.0)	6 (54.5)	45 (54.9)	0.912
6MWD, m	398.58±85.45	347.39±129.43	387.31±89.1	355.67±101.29	398.71±103.73	0.205
Laboratory tests						
FT3, pg·mL^{-1}	2.88 (2.59–3.22)	4.61 (2.95–5.9)*	2.47 (2.26–2.68)*	2.84 (2.57–3.21)	2.9 (2.64–3.14)	<0.001
FT4, ng·dL^{-1}	1.2 (1.07–1.38)	1.83 (1.3–2.62)*	0.88 (0.81–1.26)*	1.23 (1.18–1.43)	1.19 (1.08–1.31)	<0.001
TSH, mU·L^{-1}	2.22 (1.55–3.44)	0.12 (0.01–2.1)*	5.75 (4.27–11.66)*	0.37 (0.28–0.43)*	5.90 (5.16–7.31)*	<0.001
Creatinine, μmol·L^{-1}	70.48±14.12	65.09±16.51	73.94±21.87	62.68±11.98	72.34±15.25	0.066
Uric acid, μmol·L^{-1}	381.4±113.42	382.55±87.04	393.37±146.9	328.93±131.08	424.73±146.87*	0.108
Total cholesterol, mmol·L^{-1}	3.98±0.84	3.76±1.08	3.66±0.92	3.86±0.85	4.3±1*	0.008
HDL, mmol·L^{-1}	1.05±0.29	1.09±0.35	1.03±0.39	1.13±0.34	1.11±0.35	0.764
LDL, mmol·L^{-1}	2.3±0.66	2.19±0.89	2.16±0.67	2.35±0.66	2.64±0.77*	0.008
NT-proBNP, pg·mL^{-1}	512.1 (269–1159.1)	639.7 (208.1–1314)	1003.9 (305.8–2518.5)*	573.04 (251.0–1207.8)	760.7 (408.1–1536.4)*	0.239
Pulmonary function						
FEV_1, % pred	89.34±11.58	84.84±14.69	82.4±12.12	85.37±10.44	75.86±20.89*	0.138
FVC, % pred	93.53±14.53	87.94±13.79	88.2±14.15	91.11±12.65	85.2±16.72*	0.635
FEV_1/FVC, % pred	96.62±10.53	98.48±7.59	94.98±14.33	93.61±10.36	91.55±15.57	0.341
TLC, % pred	92.39±10.72	87.14±12.51	85.99±13.41	90.38±13.9	86.25±13.57*	0.813
D_{LCO}, % pred	66.08±13.67	58.92±14.22	61.66±18.03	58.94±18.15	59.25±16.28	0.948
Echocardiography						
LAAPD, mm	27.9±4.08	28.42±2.99	29.32±2.82	28.8±3.22	28.91±5.22	0.915
LVEDD, mm	35.09±6.65	37±5.86	35.72±5.33	36±4.90	34.84±7.46	0.564
LVEF, %	65.72±7.74	64.36±5.42	63.52±4.94	65.09±5.15	64.6±7.15	0.884
RVAPD, mm	34.55±10.67	31.58±6.87	32.79±6.73	33.7±5.33	34.73±7.66	0.266
Pericardial effusion	27 (21.8)	1 (4.2)	8 (32.0)	1 (10.0)	15 (20.0)	0.068
Comorbidities						
Hypertension	10 (6.8)	3 (12.5)	5 (17.9)	1 (8.3)	10 (11.9)	0.277
Arrhythmia	3 (2.0)	2 (8.3)	0	0	1 (1.2)	0.263
Diabetes	2 (1.4)	0	1 (3.6)	0	2 (2.4)	0.685

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise stated. BMI: body mass index; PH: pulmonary hypertension; WHO: World Health Organization; FC: functional classification; 6MWD: 6-min walk distance; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NT-proBNP: N-terminal pro-brain natriuretic peptide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; LAAPD: left atrial anteroposterior diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; RVAPD: right ventricular anteroposterior diameter. [#]: p-values for comparisons among subgroups of IPAH with thyroid dysfunction using ANOVA or the Kruskal–Wallis test. *: p<0.05 compared with IPAH without thyroid dysfunction.

(83.3% *versus* 32.7%; p=0.001) was better than that of IPAH patients with euthyroid function, while patients with subclinical thyroid dysfunction had comparable survival with IPAH patients (figure 1 and supplementary table S1).

Baseline variables associated with the outcome of IPAH patients were identified through Cox analysis (supplementary table S2). S_{vO_2}, RAP, CI, PVR, TPR, PAWP, NT-proBNP and PAH-targeted therapy were significantly associated with mortality and were imbalanced at baseline among groups. After adjusting for these potential confounding factors in multivariate Cox analysis, patients with hypothyroidism showed a decreased risk of mortality (hazard ratio (HR) 0.246, 95% CI 0.077–0.786), while the survival benefits of patients with other forms of thyroid dysfunction were not statistically significant (figure 2a). When reclassifying patients as IPAH with clinical thyroid dysfunction (hyper- and hypothyroidism) and

TABLE 2 Haemodynamic profiles of idiopathic pulmonary arterial hypertension (IPAH) patients with and without thyroid dysfunction

	IPAH without thyroid dysfunction	IPAH with thyroid dysfunction				p-value#
		Hyperthyroidism	Hypothyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism	
S_{vO_2}, %	66.18±9.47	72.79±7.41*	69.57±7.69	68.3±9.8	66.71±8.86	0.021
RAP, mmHg	8 (4–11.8)	4 (1.3–8.5)*	6.5 (2.3–9)	3.5 (2–10.3)	6 (2–10)*	0.512
mPAP, mmHg	57.84±14.56	54.33±17.49	53.04±16.05	50.42±9.64	58.36±13.97	0.155
Q_p/Q_s	0.91±0.39	0.92±0.18	0.95±0.17	0.92±0.07	0.93±0.12	0.853
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.27 (1.8–2.80)	2.95 (2.14–3.69)*	2.32 (2.11–3.19)	2.58 (2.48–2.82)	2.44 (1.94–2.93)	0.191
TPR, WU	15.95 (12.06–23.07)	10.29 (7.59–17.52)*	12.50 (9.1–17.92)*	12.09 (7.51–14.78)*	15.84 (11.03–21.41)	0.007
PVR, WU	13.86 (10.2–19.2)	9.14 (6.50–15.67)*	10.70 (7.51–15.21)*	11.41 (6.93–13.77)	13.28 (9.98–18.64)	0.040
PAWP, mmHg	8.86±3.76	7.48±3.33	7±3.52*	6±2.3*	7.64±3.47	0.420

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. S_{vO_2}: mixed venous oxygen saturation; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; Q_p/Q_s: pulmonary/systemic blood flow ratio; CI: cardiac index; TPR: total pulmonary resistance; WU: Wood units; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure. #: p-values for comparisons among subgroups of IPAH with thyroid dysfunction using ANOVA or the Kruskal–Wallis test. *: p<0.05 compared with IPAH without thyroid dysfunction.

subclinical thyroid dysfunction (subclinical hyper- and hypothyroidism), Cox analysis revealed that IPAH with clinical thyroid dysfunction showed better survival than those without thyroid dysfunction (HR 0.208, 95% CI 0.076–0.570) after adjusting for the same confounders, while patients with subclinical thyroid dysfunction did not show significant survival benefit (figure 2b).

Discussion

The present study first illustrated the characteristics and long-term survival of IPAH patients with different levels of thyroid dysfunction, and compared them with IPAH patients without thyroid dysfunction. This is the largest multicentre study on IPAH patients with thyroid dysfunction with the longest follow-up. Our findings may provide insights into a better understanding of the relationship between thyroid dysfunction and PAH from a clinical perspective.

In the current study, we found that IPAH patients with different levels of thyroid dysfunction showed different characteristics and outcomes compared with those with euthyroid function. An interesting finding was that IPAH patients with clinical hyper- and hypothyroidism showed better haemodynamic profiles and long-term survival than those without thyroid dysfunction. The survival benefit in patients with hypothyroidism remained after adjusting for baseline haemodynamic profiles and PAH-targeted therapy, while the survival benefit in patients with hyperthyroidism was not statistically significant. The small sample size of patients with hyperthyroidism may partly influence the statistical power, considering the wide confidence interval (HR 0.59, 95% CI 0.24–1.48). When combining patients with hyper- and hypothyroidism as one group, it was found that patients with clinical thyroid dysfunction showed significantly better survival than IPAH without thyroid dysfunction after adjustment for baseline confounding factors.

Data from the REVEAL registry showed that patients with thyroid diseases (defined as patients with hyper- or hypothyroidism and/or patients having taken synthetic thyroid replacement for hypothyroidism) had

TABLE 3 Treatment for thyroid diseases and pulmonary arterial hypertension (PAH) at baseline

	IPAH without thyroid dysfunction	IPAH with thyroid dysfunction				p-value#
		Hyperthyroidism	Hypothyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism	
Thyroid dysfunction treatment	0	12 (50.0)*	18 (64.3)*	1 (8.3)*	4 (4.8)*	<0.001
PAH-targeted therapy						0.096
None	56 (37.8)	6 (25.0)	2 (7.1)*	2 (16.7)	18 (21.4)*	
Monotherapy	84 (56.8)	18 (75.0)	19 (67.9)	8 (66.7)	51 (60.7)	
Combination therapy	8 (5.4)	0	7 (25.0)*	2 (16.7)	15 (17.9)*	

Data are presented as n (%), unless otherwise stated. IPAH: idiopathic PAH. #: p-values for comparisons among subgroups of IPAH with thyroid dysfunction using the Chi-squared test or Fisher's exact test. *: p<0.05 compared with IPAH without thyroid dysfunction.

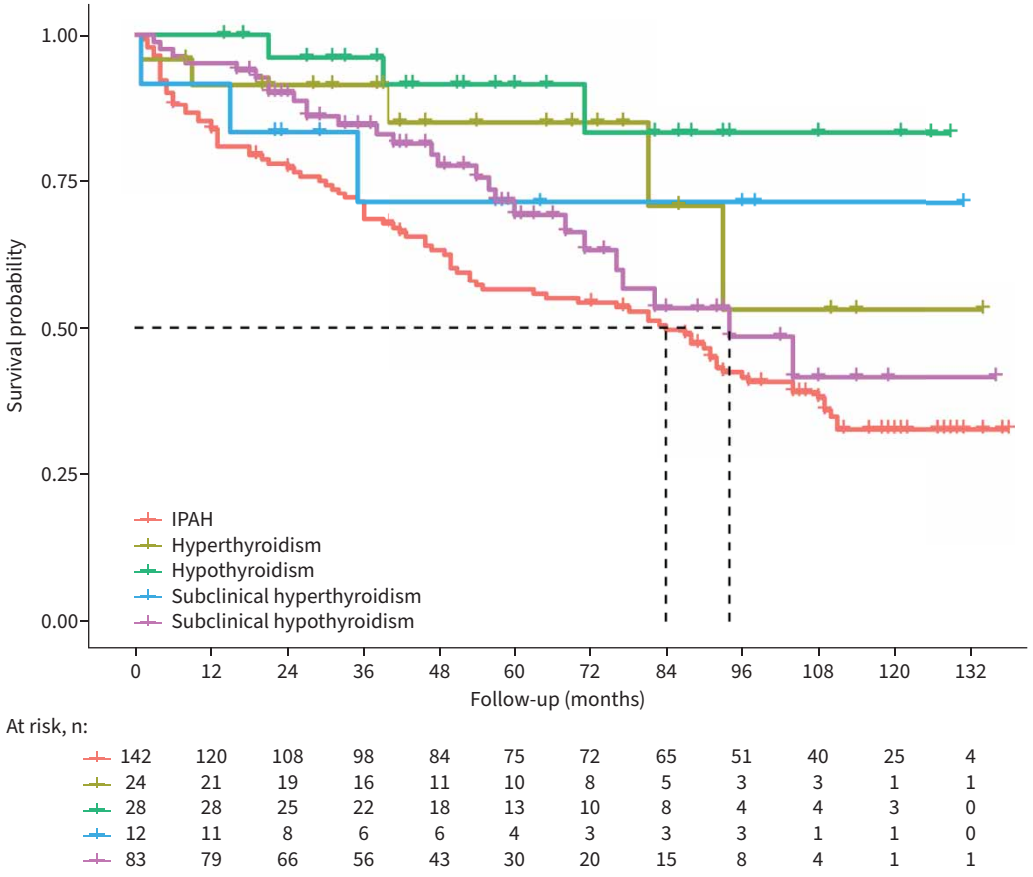

FIGURE 1 Survival curves of idiopathic pulmonary arterial hypertension (IPAH) patients with and without thyroid dysfunction.

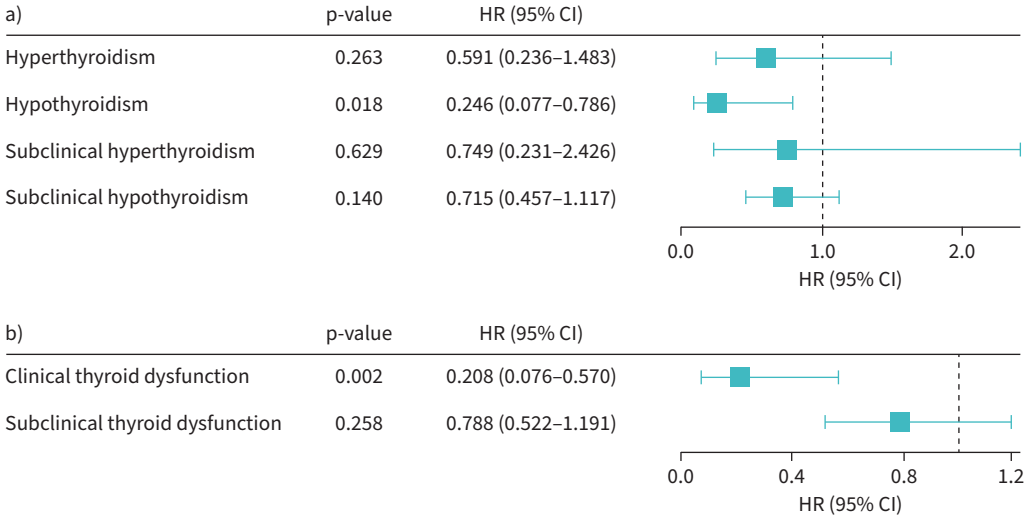

FIGURE 2 Mortality risk (hazard ratio (HR)) of idiopathic pulmonary arterial hypertension (IPAH) with different levels of thyroid dysfunction after adjustment. a) Mortality risk of IPAH with hyperthyroidism, hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism compared with IPAH without thyroid dysfunction. b) Mortality risk of IPAH with clinical and subclinical thyroid dysfunction compared with IPAH without thyroid dysfunction.

similar haemodynamics and 3-year survival compared with patients without any of the analysed comorbidities [10]. The different inclusion criteria may be one of the important reasons for the different findings in the REVEAL registry and the present study. Patients with associated PAH were excluded from our study but were included in the REVEAL registry and accounted for more than half of the patients. The existence of underlying conditions may influence the outcomes of their patients and mask the impact of thyroid dysfunction. Thus, our findings may be more reliable and representative regarding the prognostic impact of thyroid dysfunction on PAH. In addition, the demographic (younger age in our cohort) features, ethnic groups and follow-up durations may also contribute to the differences.

Case reports or series reported that in patients with pre-existing PAH, the development of hyperthyroidism may lead to acute cardiopulmonary decompensation and death [14]. However, numerous studies have shown that PAH in patients with hyperthyroidism can be improved or even reversed after the treatment of thyroid disease [15]. In the present study, 62.5% of our patients with hyperthyroidism had a history of thyroid disease before the diagnosis of PAH and half of them were treated with antithyroid drugs at baseline. For patients who were not treated for thyroid disease, the degree of hyperthyroidism was mild (median TSH 0.1 $mU \cdot L^{-1}$, FT3 5.33 $pg \cdot mL^{-1}$ and FT4 2.1 $ng \cdot dL^{-1}$). Similar conditions were also seen in patients with hypothyroidism. Thus, the relatively mild thyroid dysfunction and/or timely treatment of thyroid disease may be one of the reasons for the better prognosis in our patients with hyper- or hypothyroidism compared with other studies [14]. These findings highlighted the importance of early identification and treatment of thyroid disease in patients with PAH to maintain a stable condition and improve the prognosis.

In addition, it was found that IPAH patients with hyper- or hypothyroidism showed lower PVR and TPR than IPAH without thyroid dysfunction, suggesting less severe pulmonary vascular disease in the former. These differences may be related to different pathophysiological mechanisms in the generation of PAH between patients with clinical thyroid dysfunction and IPAH with euthyroid function. Previous studies have suggested that hyper- and hypothyroidism may participate in the development of PAH through autoimmune mechanisms, inflammatory mechanisms and the direct effects of thyroxine on the cardiovascular system, although their pathophysiological role has been poorly understood [6, 16–19]. Our findings may indicate that the possible role of thyroid dysfunction in the development of pulmonary vascular diseases is relatively benign compared with IPAH not associated with clinically manifested thyroid diseases. However, further mechanism and pathological studies are warranted to confirm our findings.

Furthermore, an alternative explanation for better haemodynamics and survival in clinical hyper- or hypothyroidism may be related to a detection and lead-time bias. These patients may be identified at an earlier stage of their pulmonary vascular disease courses, as their thyroid disease makes them more symptomatic despite milder pulmonary vascular disease, or just being detected occasionally during more frequent medical follow-ups due to thyroid disease.

Subclinical hypothyroidism was the most common type of thyroid dysfunction in our patients, accounting for 56.8% of patients with thyroid dysfunction. This is consistent with previous findings in patients with PH [4]. Importantly, these patients showed the worst haemodynamics and survival among patients with thyroid dysfunction but were comparable with IPAH patients with euthyroid function. In patients with subclinical hypothyroidism, more patients were previously diagnosed with PAH, which meant that the disease duration of PAH in these patients was longer. In addition, higher levels of total cholesterol and LDL were found in IPAH with subclinical hypothyroidism and the pulmonary function was more severely impaired. These findings may suggest potential multiorgan dysfunction and metabolic dysfunction caused by long-term chronic PAH and cardiac dysfunction. Higher NT-proBNP and more frequently used combination therapy in our patients with subclinical hypothyroidism also indicated more severe disease in these patients. Studies have shown that thyroid abnormalities can be seen in critically ill patients [20, 21]. It seems that the presence of subclinical hypothyroidism is more likely to be a pathophysiological manifestation in the advanced course of IPAH, as a part of multiorgan dysfunction, or associated with systemic stress or systemic vulnerability in critical patients, as indicated in the recent work of Pı *et al*. [22]. This can also explain the worst prognosis of patients with subclinical hypothyroidism among patients with thyroid dysfunction, despite relatively aggressive treatment of PAH.

There are several limitations in the present study. First, the total number of PAH patients with thyroid dysfunction was limited and subclinical hypothyroidism accounted for the majority of our patients, resulting in small sample sizes of other subgroups; this may have influenced the statistical power. Therefore, the findings of our study should be interpreted with caution. These results should be considered as preliminary signs of evidence and hypothesis generating, rather than definitive validated conclusions.

However, this is the largest study on IPAH patients with different types of thyroid dysfunction, which helps with a better understanding of thyroid dysfunction and PAH after ruling out the confounding effects of underlying diseases of PAH. Second, the specific aetiologies of thyroid dysfunction and autoimmune antibodies of the thyroid were not recorded in our registry. Thus, we were unable to explore the influence of different aetiologies of thyroid disease on PAH. Further studies are needed to consider the role of thyroid and systemic autoimmunity and better understand the mechanism of the frequent co-occurrence of PAH and thyroid disease, as well as the effect of different thyroid disease aetiologies on outcomes of PAH patients [23]. Third, the follow-up data on thyroid function were not recorded in our registry. Therefore, the development of thyroid dysfunction during follow-up was unclear in our patients. The change in thyroid function may influence the prognosis of the patients. Lastly, it should be noted that the patients included in our study were thoroughly evaluated to exclude known aetiologies of PAH and Group 2–5 PH; therefore, generalisation of our findings to PAH patients with associated conditions or other groups of PH should be done with caution.

In conclusion, IPAH patients with clinical hyper- and hypothyroidism had better haemodynamic profiles and survival than those without thyroid dysfunction. However, IPAH patients with subclinical hypothyroidism showed similar haemodynamics and survival compared with IPAH patients with euthyroid function. Further pathophysiological studies are needed to confirm the exact association between thyroid disease and PAH.

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Data availability: The datasets generated and analysed during the current study are not publicly available due to regulations on the management of human genetic resources/data of our hospital.

Ethics statement: The study protocol was approved by the Review Board of Fuwai Hospital, Beijing, China (approval number 2009-208).

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