



# Thyroid-stimulating hormone and mortality in pulmonary arterial hypertension

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**To cite:** Pi H, Rayner SG, Ralph DD, *et al*. Thyroid-stimulating hormone and mortality in pulmonary arterial hypertension. *BMJ Open Resp Res* 2022;**9**:e001348. doi:10.1136/bmjresp-2022-001348

Received 27 June 2022  
Accepted 4 July 2022

## ABSTRACT

**Introduction** Pulmonary arterial hypertension (PAH) remains a serious and life-threatening illness. Thyroid dysfunction is relatively understudied in individuals with PAH but is known to affect cardiac function and vascular tone in other diseases. The aim of this observational study was to evaluate the association between thyroid-stimulating hormone (TSH), mortal and non-mortal outcomes in individuals with PAH.

**Methods** The Seattle Right Ventricle Translational Science (Servetus) Study is an observational cohort that enrolled participants with PAH between 2014 and 2016 and then followed them for 3 years. TSH was measured irrespective of a clinical suspicion of thyroid disease for all participants in the cohort. Linear regression was used to estimate the relationships between TSH and right ventricular basal diameter, tricuspid annular plane systolic excursion and 6-minute walk distance. Logistic regression was used to estimate the relationship with New York Heart Association Functional Class, and Cox proportional hazards were used to estimate the relationship with mortality. Staged models included unadjusted models and models accounting for age, sex at birth and aetiology of pulmonary hypertension with or without further adjustment for N-terminal-pro hormone brain natriuretic peptide.

**Results** Among 112 participants with PAH, TSH was strongly associated with mortality irrespective of adjustment. There was no clear consistent association between TSH and other markers of severity in a cohort with PAH.

**Discussion** This report reinforces the important observation that TSH is associated with survival in patients with PAH, and future study of thyroid dysfunction as a potential remediable contributor to mortality in PAH is warranted.

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare but serious disease leading to progressive right heart failure and death. Thyroid hormone impacts cardiac contractility, cardiac output, pulmonary and systemic vascular resistance,<sup>1,2</sup> and up to 20%–25% of patients with PAH have comorbid thyroid disease.<sup>3–7</sup> This raises the question of whether thyroid dysfunction may impact the clinical course

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous work has suggested thyroid-stimulating hormone (TSH) is associated with mortality in patients with pulmonary arterial hypertension (PAH); however, this evidence is limited to a single institution cohort and has not been replicated.

## WHAT THIS STUDY ADDS

⇒ The current study validates a strong association between TSH and mortality in individuals with PAH in a second cohort and is the first to consider whether TSH is associated with other metrics of severity in PAH.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study are hypothesis generating and continue to support ongoing investigation into thyroid dysfunction as a potential remediable factor for patients with PAH.

of PAH. Despite evidence linking thyroid dysfunction with the diagnosis of pulmonary hypertension, there is limited evidence exploring the relationship between thyroid dysfunction and PAH outcomes.<sup>7</sup> We hypothesised that elevated thyroid-stimulating hormone (TSH), a screening marker for thyroid dysfunction, would be associated with worse clinical outcomes in PAH.

## METHODS

The Seattle Right Ventricle Translational Science (Servetus) Study is a prospective observational cohort of participants with PAH followed at the University of Washington Medical Center. Participants were enrolled from 2014 to 2016 and followed for at least 3 years. All participants contributed to an imaging and blood-based biorepository. For this study, TSH was measured using banked blood on all participants independent of clinical suspicion for thyroid dysfunction. Patients were stratified into three subgroups:



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normal TSH (0.6–4.5 mIU/L), low TSH ( $\leq 0.5$  mIU/L) and high TSH ( $>4.5$  mIU/L).

Demographic data including age, sex at birth, height and weight were recorded. Aetiology of PAH (ie, connective tissue disease, familial, idiopathic, etc) was adjudicated by investigators. New York Heart Association (NYHA) Functional Class, N-terminal-pro hormone brain natriuretic peptide (NT-proBNP), 6-minute walk distance (6MWD), demographics and aetiology were recorded at the time of enrolment. Transthoracic echocardiogram (TTE) results (including right ventricular (RV) basal diameter and tricuspid annular plane systolic excursion (TAPSE)) were collected within 3 months of enrolment.

Cox proportional hazards estimated the association between TSH and mortality; linear regression estimated associations with TTE parameters and 6MWD; and logistic regression estimated the association with a poor NYHA Functional Class (III/IV). Staged models were used to understand impacts from potential confounders. Adjusted models included age, sex and PAH aetiology. NT-proBNP was included in an additional model to understand whether relationships were dependent on a known marker of right heart failure severity. All analyses were performed using Stata V.15.0 (StataCorp., College Station, Texas, USA). Two-sided statistical tests with a *p* value of  $<0.05$  were defined as significant.

### Patient and public involvement

The prospective Servetus cohort was developed with input from leading patient advocacy organisations.

### RESULTS

A total of 112 patients were included (table 1). High TSH was associated with significantly higher mortality (tables 2 and 3). Accounting for differences in age, sex, PAH aetiology and NT-proBNP did not meaningfully change this relationship. Low TSH was not associated with mortality. TSH levels were not associated with significant differences in other markers of severity including RV basal diameter, TAPSE, 6MWD or NYHA Functional Class (table 2). There was concern that the stratified approach might overweight the impact of six participants with high TSH. A separate approach modelled TSH as a continuous variable (instead of clinical strata) or as log-transformed using linear regression to better account for the relationship in the full cohort and had a similar relationship such that high TSH continued to be associated with increased mortality (table 3).

### DISCUSSION

Despite several reports detailing connections between thyroid disease and the initial diagnosis of pulmonary hypertension,<sup>2–7</sup> associations between thyroid dysfunction and the clinical course in patients with PAH are less well studied. Only one previous study addressed the association of TSH and outcomes in PAH.<sup>7</sup> Like this previous

**Table 1** Baseline characteristics

n	112
Demographics	
Age (years)	52±14
Height (cm)	164±18
Weight (kg)	80±22
Body mass index (kg/m <sup>2</sup> )	29.1±7.3
Female	93 (83%)
White	100 (89%)
Aetiology	
Idiopathic or familial	45 (40%)
Methamphetamine associated	20 (18%)
Connective tissue disease associated	27 (24%)
Congenital heart disease associated	20 (18%)
Haemodynamics	
Right atrial pressure (mm Hg)	9±6
Mean pulmonary artery pressure (mm Hg)	47±13
Cardiac index (L/min/m <sup>2</sup> )	2.6±0.8
Pulmonary vascular resistance (Wood units)	8.6±4.8
Markers of severity	
6MWD (m)	366±107
RV basal diameter (cm)	4.5±0.8
TAPSE (mm)	20±5
NYHA Functional Class III/IV	38 (34%)
Treatment	
PAH monotherapy	39 (35%)
PAH dual-agent therapy	54 (48%)
PAH triple-agent therapy	19 (17%)
Thyroid replacement therapy	16 (14%)
Treatment for hyperthyroidism	0 (0%)
6MWD, 6-minute walk distance; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.	

report from Giessen, we found an association between elevated TSH and a substantially higher risk of mortality.

In addition to reinforcing the limited previous results regarding mortality, we are the first to explore the relationship of TSH with non-mortal markers of severity. We did not find a clear association with these metrics. The strict interpretation of these results, which lacked consistent statistically significant associations between TSH and non-mortal markers of PAH severity, might suggest that the excess mortality is not explained by progressive right heart failure. This hypothesis may be supported by the observation that the association between high TSH and mortality was independent of NT-proBNP, a marker of right heart failure in PAH. In this line of thinking, elevated TSH could be a marker or mediator of systemic stress or a systemic vulnerability that is not specific to the cardiopulmonary axis.<sup>8</sup> Less than half of patients with PAH die from progressive right heart failure<sup>9</sup> and TSH may reflect systemic vulnerabilities or a composite marker of systemic stress that is not otherwise well captured by

**Table 2** Association between TSH and markers of disease severity

	Relative to normal TSH (n=96)			
	Low TSH (n=10)		High TSH (n=6)	
	95% CI	P value	95% CI	P value
<b>Hazard of mortality</b>				
Unadjusted	0.7 (0.1 to 5.0)	0.69	<b>4.5 (1.3 to 15.7)</b>	<b>0.02</b>
Full	0.8 (0.1 to 6.5)	0.84	<b>7.1 (1.8 to 28.5)</b>	<b>0.006</b>
Full+NT-proBNP	1.7 (0.2 to 14.2)	0.64	<b>5.2 (1.2 to 22.4)</b>	<b>0.03</b>
<b>RV basal diameter (cm)</b>				
Unadjusted	-0.3 (-1.0 to 0.3)	0.32	0.3 (-0.5 to 1.1)	0.47
Full	-0.3 (-0.9 to 0.3)	0.29	0.3 (-0.4 to 1.1)	0.40
Full+NT-proBNP	-0.2 (-0.7 to 0.4)	0.58	-0.1 (-0.7 to 0.4)	0.80
<b>TAPSE (mm)</b>				
Unadjusted	3 (-1 to 7)	0.14	-4 (-9 to 1)	0.15
Full	3 (0 to 7)	0.08	-4 (-9 to 1)	0.14
Full+NT-proBNP	3 (-1 to 7)	0.14	-2 (-7 to 3)	0.41
<b>Walk distance (meters)</b>				
Unadjusted	64 (-9 to 137)	0.09	-84 (-171 to 4)	0.06
Full	62 (-13 to 136)	0.10	-75 (-163 to 14)	0.10
Full+NT-proBNP	56 (-11 to 122)	0.10	-16 (-99 to 66)	0.70
<b>NYHA Functional Class</b>				
Unadjusted	0.9 (0.2 to 4.7)	0.85	4.3 (0.7 to 24.8)	0.11
Full	0.8 (0.1 to 4.7)	0.78	4.5 (0.6 to 31.5)	0.13
Full+NT-proBNP	0.9 (0.1 to 7.7)	0.92	3.3 (0.4 to 30.3)	0.30

Full model accounted for differences in age, sex at birth and aetiology of pulmonary hypertension. Hazard of mortality was estimated using Cox proportional hazards, RV basal diameter/TAPSE/walk distance were estimated using linear regression, the odds of NYHA Functional Class of III/IV relative to I/II were estimated using logistic regression. Coefficients represent relationships between participants with high or low TSH relative to normal TSH (0.5–4.0). Value in bold indicates statistically significant results. NT-proBNP, N-terminal-pro hormone brain natriuretic peptide; NYHA, New York Heart Association; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TSH, thyroid-stimulating hormone.

cardiac-specific metrics, such as that seen with sick euthyroid syndrome.

Alternatively, the lack of associations between TSH and non-mortal markers of PAH severity may reflect insufficient power. Notably, point estimates between non-mortal markers of severity consistently suggest the possibility of worse disease with high TSH. If the trends are correct (and the lack of significance merely reflects insufficient power), then TSH may remain a marker or mediator specific to the cardiopulmonary axis in patients with PAH. This explanation is tempting to suspect as thyroid hormone is known to affect the cardiovascular system both directly and indirectly.<sup>1 10</sup>

**Table 3** Association between TSH and markers of disease severity

	Per SD		Per log change in TSH	
	95% CI	P value	95% CI	P value
	<b>Hazard of mortality</b>			
Unadjusted	<b>1.3 (1.0 to 1.8)</b>	<b>0.05</b>	<b>1.9 (1.0 to 3.6)</b>	<b>0.05</b>
Full	<b>1.4 (1.1 to 2.0)</b>	<b>0.02</b>	<b>2.1 (1.0 to 4.2)</b>	<b>0.05</b>
Full+NT-proBNP	1.4 (1.0 to 2.0)	0.08	1.7 (0.8 to 3.6)	0.18
<b>RV basal diameter (cm)</b>				
Unadjusted	0.1 (-0.1 to 0.3)	0.18	<b>0.2 (0.0 to 0.4)</b>	<b>0.02</b>
Full	0.1 (-0.1 to 0.3)	0.23	<b>0.2 (0.0 to 0.4)</b>	<b>0.02</b>
Full+NT-proBNP	0.0 (-0.1 to 0.2)	0.82	0.1 (0.0 to 0.3)	0.14
<b>TAPSE (mm)</b>				
Unadjusted	-1 (-2 to 0)	0.17	-1 (-2 to 0)	0.07
Full	-1 (-2 to 0)	0.13	<b>-1 (-2 to 0)</b>	<b>0.02</b>
Full+NT-proBNP	-1 (-2 to 1)	0.34	-1 (-2 to 0)	0.09
<b>Walk distance (m)</b>				
Unadjusted	-14 (-35 to 6)	0.17	-19 (-43 to 5)	0.11
Full	-12 (-33 to 9)	0.25	-17 (-41 to 7)	0.16
Full+NT-proBNP	-1 (-20 to 18)	0.92	-7 (-29 to 15)	0.55
<b>NYHA Functional Class</b>				
Unadjusted	1.3 (0.9 to 2.0)	0.21	1.3 (0.8 to 2.2)	0.27
Full	1.4 (0.9 to 2.2)	0.19	1.4 (0.8 to 2.5)	0.19
Full+NT-proBNP	1.2 (0.7 to 2.0)	0.44	1.2 (0.7 to 2.3)	0.51

Full model accounted for differences in age, sex at birth and aetiology of pulmonary hypertension. Hazard of mortality was estimated using Cox proportional hazards, RV basal diameter/TAPSE/walk distance were estimated using linear regression, the odds of NYHA Functional Class of III/IV relative to I/II were estimated using logistic regression. Coefficients represent relationships for an SD difference in TSH. Value in bold indicates statistically significant results. NT-proBNP, N-terminal-pro hormone brain natriuretic peptide; NYHA, New York Heart Association; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TSH, thyroid-stimulating hormone.

There are clear limitations in this study. First, there was no differentiation between overt thyroid disease and subclinical thyroid dysfunction in this analysis. Our study focused on TSH as a broad screening tool for thyroid dysregulation rather than characterising specific aspects of thyroid dysfunction. Additionally, observational studies always have the potential for residual and unmeasured confounding. While we discuss potential mechanistic explanations for our findings, these are speculative.

Despite limitations, our data join a previous cohort<sup>7</sup> to suggest that high TSH levels are associated with worse all-cause mortality in patients with PAH. Thyroid disease is relatively common, remediable and easily studied. The



lack of a larger definitive study in individuals with PAH is notable. Additional study is warranted to determine whether overt thyroid disease drives the association with mortality in individuals with PAH, whether the association is mediated by PAH severity, and/or whether TSH is a marker of other systemic vulnerabilities.

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**Contributors** HP and PL performed the primary analyses and drafted the manuscript. All authors contributed to cohort development, made revisions to the final manuscript and approved the manuscript for publication. PL is responsible for the overall content of the work.

**Funding** This publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award KL2TR000421.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by the University of Washington (IRB approval #3387). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data are available upon reasonable request to the corresponding author.

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