

Who should be referred to a specialist pulmonary hypertension centre – a referrer's guide

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ABSTRACT

The introduction of pulmonary hypertension (PH)-specific drugs has allowed certain forms of PH to become more treatable. However, patients with these diseases can present to a number of medical specialties and can be challenging to identify, particularly in a non-specialist setting. This article provides guidance on who should be investigated and referred on to a specialist centre, highlighting the potential pitfalls during assessment.

KEYWORDS: Pulmonary hypertension, chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension, screening, assessment

Introduction

Pulmonary hypertension (PH) is defined as an elevated mean pulmonary artery pressure (mPAP) ≥ 25 mmHg¹ at right heart catheterisation (RHC), and is characterised by progressive dyspnoea, presyncopal symptoms, chest pain and peripheral oedema due to a failing right ventricle (RV). Although many causes of PH exist, some have become more treatable, particularly since oral pulmonary arterial hypertension (PAH)-specific drug therapy was introduced. In parallel, surgical advances have significantly improved outcomes for chronic thromboembolic pulmonary hypertension (CTEPH), allowing many patients to undergo curative pulmonary endarterectomy (PEA) surgery.

As untreated PH carries a poor prognosis, potentially treatable patients should be identified early. However, many wait 1–4 years from symptom onset until PH is diagnosed,² with national data demonstrating wide variation in diagnostic rates across the UK.³ Conversely, as awareness has increased so has the number of patients inappropriately referred to specialist centres, with 28% of referrals ultimately not having PH and a further 24%

having PH associated with left heart or lung disease.³ As these patients will not respond to PH-specific therapy this results in unnecessary investigations, often long-distance travel and falsely elevated expectations while impairing the ability of specialist centres to handle more suitable cases.

Identifying patients appropriate for referral can be challenging, particularly in a non-specialist setting. This article offers guidance for referrers and is based on experience gained by the authors who have developed a shared care PH service in a district general hospital setting since 2005.

Classification of PH

The classification of PH is regularly modified as our understanding of patient phenotypes improves. The current classification is adapted from the Fifth World Symposium (Box 1).⁴ Here PH is classified according to a shared underlying pathophysiology and approach to therapy. In general, only patients with PAH (group 1) and CTEPH (group 4) respond to PH-specific therapy and thus warrant referral to a specialist centre.

PAH is characterised by a pulmonary vasculopathy that causes a progressive rise in pulmonary vascular resistance (PVR), and hence mPAP. PAH often develops in the context of another systemic disease or through exposure to an appropriate precipitant (Box 1). Where there is no identifiable predisposing factor, patients are diagnosed with idiopathic PAH. All group 1 diseases can potentially respond to PAH-licensed medical therapies which are thought to target the underlying pulmonary vasculopathy.

CTEPH is characterised by partial obstruction of the pulmonary arteries by chronic thrombus. The condition likely represents a rare complication of acute pulmonary embolic disease, although only 75% of patients have a documented preceding event.⁵ The treatment of choice is PEA, which can be curative when the disease is situated proximally within the pulmonary arteries. Pulmonary vasodilators have until recently only been demonstrated to be of benefit in group 1 PAH but recently randomised control trial data have shown a role for riociguat in distal and inoperable CTEPH.⁶

PH services in the UK

PH services in the UK are delivered through a network of seven specialist centres, including one that provides a national PEA

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Box 1. Updated clinical classification of pulmonary hypertension. Reproduced with permission.⁴

Group 1: PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
 - 1.2.1 Bone morphogenic protein receptor type II
 - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
 - 1.2.3 Unknown
- 1.3 Drug and toxin induced (eg anorexigens, amphetamines)
- 1.4 Associated with:
 - 1.4.1 connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 portal hypertension
 - 1.4.4 congenital heart disease
 - 1.4.5 schistosomiasis

1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1'' Persistent pulmonary hypertension of the newborn

Group 2: Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

Group 4: Chronic thromboembolic pulmonary hypertension

Group 5: Pulmonary hypertension with unclear multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

service for operable CTEPH. This unique network approach allows the UK to offer a standardised approach to treatment, audit and research that has driven international understanding of these rare diseases. Although this approach has been successful, centralisation potentially disadvantages some areas of the country. Recognising this, several shared care services have been developed that deliver components of PH care locally with specialist centre oversight.

Bath has offered a shared care service with the Royal Free London since 2005. The service has steadily grown and now manages 150 referrals/year through a multidisciplinary approach involving the local respiratory, cardiology, rheumatology and radiology departments.

PAH and CTEPH are probably underdiagnosed

PAH and CTEPH are uncommon diseases, with an annual incidence of 2.4–7.6 cases/million^{7,8} and 1.75 cases/million⁹ respectively. However, the evidence suggests many more cases remain undiagnosed. PAH prevalence varies across the UK (Fig 1) with low diagnosis rates more likely to occur in areas distant from a specialist centre. At a local level, the Bath PH service has seen a marked increase in the prevalence of PAH and CTEPH in its immediate catchment area since the introduction of a shared care service and the subsequently heightened local awareness – in the Bath area alone (population ~450,000)

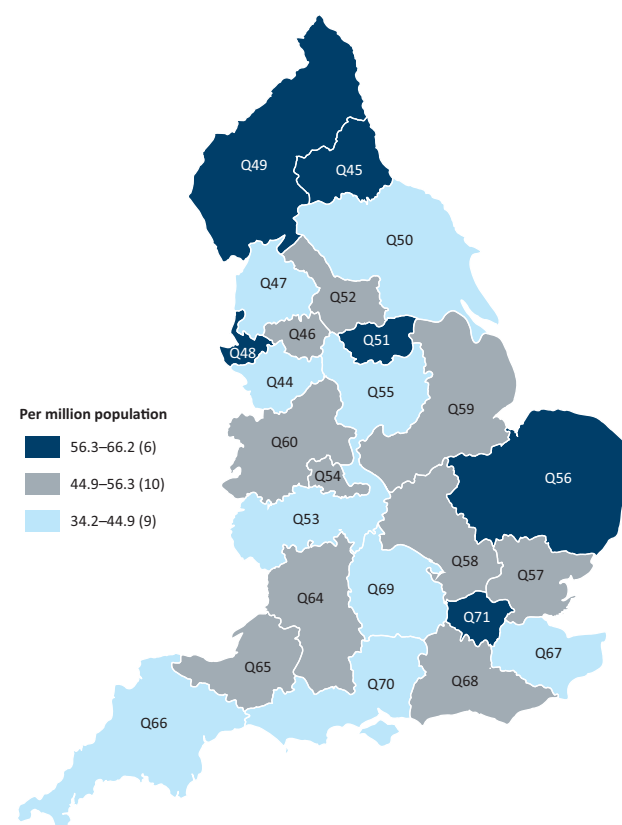


Fig 1. PAH prevalence across the UK. The numbers in parentheses show the number of local area teams which fall within the range. PAH = pulmonary arterial hypertension. Reproduced with permission of the Health and Social Care Information Centre.³

CTEPH cases have risen from 4.9 cases/million pre-2005 to 63.4 cases/million post-2005, with 13 patients undergoing PEA surgery during this time.

These observations suggest large numbers of potentially treatable PH cases go undiagnosed each year. Identifying these patients and referring them on to a specialist service would clearly be advantageous.

What is the level of clinical suspicion for PAH or CTEPH?

One of the challenges in PH is that a definitive diagnosis cannot be made without resorting to RHC. Non-invasive screening investigations are therefore used despite significantly high false-negative and false-positive rates. It is therefore important to consider the pre-test probability of treatable PH, before embarking on testing.

The cardinal symptom of PH, exertional dyspnoea, is non-specific and common to many cardiopulmonary disorders. If routine cardiopulmonary investigations, such as echocardiography, lung function tests and computed tomography (CT), indicate an alternative, more likely, explanation for a patient's breathlessness then a diagnosis of PAH or CTEPH need not be pursued.

Conversely, several systemic diseases are associated with PAH and CTEPH (Table 1),^{10–16} and thus a higher index of suspicion and a lower threshold for investigation is required when these patients present with unexplained breathlessness. This alone may warrant RHC, even if non-invasive investigations initially appear reassuring.

Can the patient's clinical presentation help?

Exertional dyspnoea is not unique to PH. However, some additional features can help distinguish PH from other cardiopulmonary diseases. Breathlessness in PH is initially innocuous, but progressive over time. Dyspnoea is consistent, rather than variable, and not commonly associated with other symptoms such as cough or wheeze. As PH progresses, further symptoms often emerge, including fluid retention as the RV fails, presyncope on extreme exertion as the RV becomes unable to increase cardiac output in response to demand, palpitations

as the heart becomes more susceptible to arrhythmias, and exertional angina as the hypertrophied RV's increasing metabolic requirements outstrip its supply.

Many of the symptoms described above only develop once a patient has advanced disease. Clinicians must therefore be vigilant early, particularly in at-risk groups. In diseases where prevalence of PAH is particularly high, eg systemic sclerosis, screening is recommended, even in the absence of symptoms.¹⁷

How helpful is echocardiography?

Although echocardiography is a key screening tool for detecting PH it is important to appreciate its limitations to avoid over- and under-diagnosing disease.

One of the most used parameters is the estimated pulmonary arterial systolic pressure (PASP), derived from the tricuspid regurgitant jet velocity. As this estimates pulmonary artery systolic pressure, the threshold for detecting PH at echocardiography (ie PASP ≥ 40 mmHg) differs from the RHC-driven mean pulmonary artery pressure threshold used to definitively diagnose PH (ie mPAP ≥ 25 mmHg). Although PASP is a helpful measure it carries many limitations. First, PASP is subject to inter-observer variability and cannot be measured in 20–39% of patients, particularly when tricuspid regurgitation is not present.^{18,19} Second, some patients are poor echocardiography subjects as a result of body habitus or co-existing comorbidities, including lung disease, resulting in inaccurate PASP estimates.²⁰ Third, although PASP at echocardiography correlates well with mPAP, receiver operating characteristic analyses suggest it is difficult to set a threshold that carries both satisfactory sensitivity and specificity.

Other more detailed parameters can be used to assess the right heart such as TAPSE (abnormal if < 2.0 cm)²¹ and pulmonary acceleration time (abnormal if < 105 msec).²²

Given these limitations, other echocardiographic signs suggestive of PH should be sought. Right atrial and ventricular dilatation in the presence of a normal left atrium and ventricle is suggestive of significant PH, regardless of PASP measurements. Similarly, septal wall encroachment into the left ventricle LV due to RV overload is seen in advanced PH. Again, these features can often be absent and thus, if a high clinical suspicion of PAH or CTEPH is present, a normal echocardiography report alone should not preclude further assessment.

The addition of an electrocardiogram (ECG) and N-terminal prohormone brain natriuretic peptide (NT-pro BNP) to echocardiography can improve the specificity for detecting pulmonary hypertension.^{17,23}

Other non-invasive investigations

Several other non-invasive tools can highlight potential PAH and CTEPH and help determine whether to proceed to more invasive investigations. However, none of these investigations carry high specificity and thus should not be relied on to exclude PH.

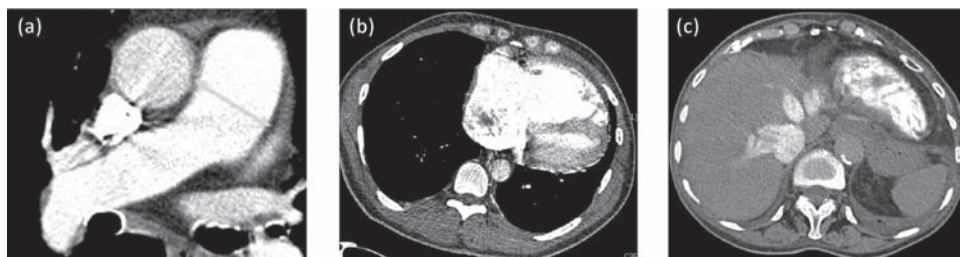
Full lung function testing typically demonstrates preserved lung volumes (ie forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC)) and an isolated reduction in carbon monoxide diffusing capacity. Patients with PH in the

Table 1. Prevalence of PH in common disease states.^{10–16}

Condition	Prevalence of PAH or CTEPH, %
PAH	
Systemic sclerosis	7–12 ^{10,11}
HIV	0.1–0.5 ¹²
Portal hypertension	1–2 ¹³
Adult congenital heart disease	6 ¹⁴
CTEPH	
Post acute PE	1–4 ^{15,16}

CTEPH = chronic thromboembolic pulmonary hypertension; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PE = pulmonary embolism; PH = pulmonary hypertension.

Fig 2. Non-specific signs of PH on CTPA. (a) Enlarged main pulmonary artery; (b) enlarged right heart; (c) hepatic reflux of contrast into IVC and hepatic veins. CTPA = computed tomography pulmonary angiography; IVC = inferior vena cava; PH = pulmonary hypertension.



context of significantly impaired lung volumes are likely to have PH secondary to lung disease (group 3) and are unlikely to respond to PH-specific therapy. Brain natriuretic peptide (BNP) is a cardiac hormone released in response to cardiac stretch, and thus increases with both right and left ventricular failure. BNP is often raised in PH, although it is neither sensitive nor specific enough to be used in isolation. ECG changes indicative of PH can include sinus tachycardia, right axis deviation, right bundle branch block, RV hypertrophy and right heart strain, but is often normal in early PH. Chest X-rays are often also normal, although cardiomegaly, prominent pulmonary arteries and peripheral pruning may be present. Autoimmune profile testing may highlight latent connective tissue diseases which can increase the level of suspicion for PAH. Ventilation perfusion (VQ) scanning is highly sensitive for identifying CTEPH, but lacks specificity, particularly in the presence of other lung pathology. A normal VQ scan effectively excludes CTEPH.

CT imaging – make the most of your radiologist

CT pulmonary angiography may offer the first opportunity to identify PH, either by demonstrating signs suggestive of elevated PAP and/or by identifying specific signs suggestive of PAH or CTEPH.

Signs of PH

An enlarged main pulmonary artery (PA) >33 mm (Fig 2a) and/or a PA:aorta ratio >1.1 both correlate strongly with elevated PAP.²⁴ Right atrial and ventricular enlargement (Fig 2b) are present when the transverse diameter of the right atrium is >35 mm and RV >45 mm, respectively.²⁵ Tricuspid regurgitation (Fig 2c) is identified by opacification of the inferior vena cava or hepatic veins on contrast-enhanced CT. A bowed interventricular septum suggests right heart strain. Atrial septal defects, ventricular septal defects, anomalous venous drainage and patent ductus arteriosus can occasionally be visualised on a contrast-enhanced CT (Fig 3a).

Signs of CTEPH

A patient with CTEPH will usually show the non-specific signs of PH described above. Additionally, intimal wall thrombus (Figs 3b and c), webs (Fig 3d) and occlusions (Fig 3e) will be present within the pulmonary vasculature. Mosaicism and peripheral scarring can be seen within the lungs due to

patchy perfusion and old infarction respectively (Fig 3f). Not uncommonly, webs and occlusions are missed or mosaicism is misdiagnosed as air-trapping; if there is doubt, especially if the patient has non-specific signs of PH on CT, then a VQ should be requested.²⁶

Other changes

In PAH the lung parenchyma typically appears normal. In some cases however, small, ill-defined ground-glass nodules are present and can be mistaken for early interstitial lung disease. Rarely, patients can present with a vasculopathy that predominantly affects the pulmonary venous system – pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis. In these uncommon diseases, there is a lack

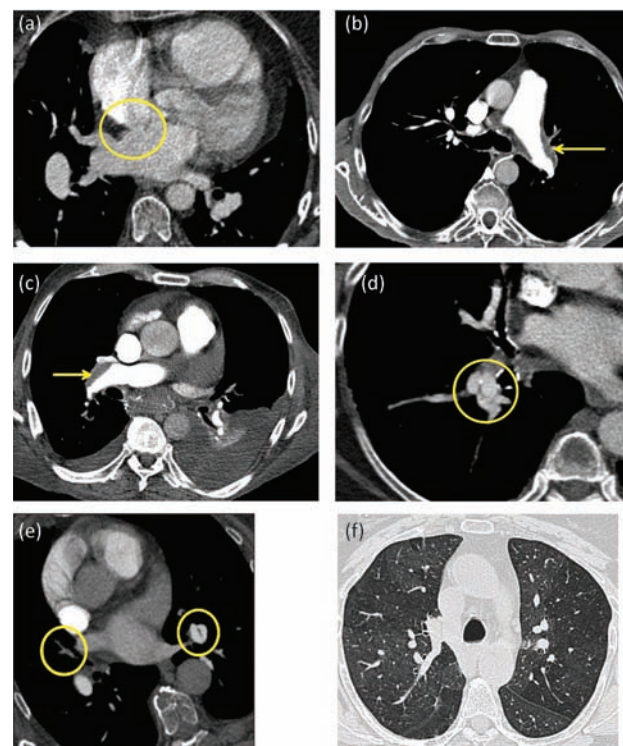


Fig 3. Specific signs of PH on CTPA. (a) Atrial septal defect; (b) and (c) proximal laminated thrombus in CTEPH; (d) webs in CTEPH; (e) occlusion in middle lobe and web in lingular; (f) mosaicism. CTEPH = chronic thrombo-embolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; PH = pulmonary hypertension.

of effective 'run-off' from the capillary bed and thus congestion ensues, causing interstitial oedema, ground-glass changes, septal thickening, effusions and adenopathy.

Streamlining referrals: early identification of PH associated with left heart disease or lung disease

PH associated with left heart disease

Any pathology that elevates left atrial filling pressures can lead to increased PAP through passive transmission of elevated left-sided pressures through the pulmonary circulation. This is associated with an elevated wedge pressure reading, but normal PVR, at RHC. Occasionally however, this can also trigger a reactive PA vasculopathy, resulting in an elevated PVR in the context of a raised wedge pressure.

Although the presence of PH increases morbidity and mortality in patients with left heart pathology, all trials of PH-specific therapy in this patient group have been negative.^{27,28} PH-specific therapy is therefore not licensed or funded for use in these patients and should only be considered within a trial setting.

As there are significant numbers of patients with left heart pathology it is important to identify these patients early. While identifying patients with impaired LV systolic function and/or significant valvular disease at ECG is relatively straightforward, most patients with PH due to left heart disease have heart failure with preserved ejection fraction, which can be difficult to diagnose. However, these patients typically share a number of features that distinguish them from PAH or CTEPH (Table 2).

PH due to lung disease

Significant lung disease can cause PH through hypoxic vasoconstriction, pulmonary vascular destruction and pulmonary vascular remodelling. Although the presence of PH adversely affects morbidity and mortality, PH due to lung disease does not respond to PH-specific therapy – indeed these agents can worsen hypoxia by encouraging shunting. PH-specific therapy is therefore not licensed or funded for use in the setting of significant lung disease, except within a trial.

Patients with suspected PH due to lung disease typically fall within four groups. The majority of patients have significant lung disease (eg FEV₁ <60% in chronic obstructive pulmonary disease, FVC <70% in pulmonary fibrosis and/or significant airway/parenchymal changes on CT) and concomitant, appropriate, modest PH (eg raised pressures at echocardiography with a normal sized RV and preserved RV function). Rather than referring these patients to a specialist centre, the focus should be on optimising their underlying lung disease and correcting resting hypoxia.

The second patient group have mild lung disease but significant PH. Given that lung disease is common, patients with significant PH in the setting of mild lung disease only may have dual pathology and require further assessment. If investigations continue to suggest PH disproportionate to the severity of the underlying lung disease, coexistent PAH and mild lung disease may be present. Of note, PAH patients often see a number of healthcare professionals before a correct diagnosis is reached and thus may be misdiagnosed with a lung disease along their referral pathway. This reinforces the importance of fully assessing for lung disease during a PH work-up.

A small proportion of patients with severe lung disease go on to develop significant PH, with severely elevated right-sided pressures and impaired cardiac function. There are no licensed therapies for these patients, although some specialist centres may recruit such patients to trials.

Finally, significant PH can be associated with rare diseases (group 5; Box 1). No robust evidence exists for PH-specific therapy in these patients, and is unlikely to be forthcoming, given the paucity of cases. This group is challenging; PDE-5 inhibitors have shown an increased rate of sickle crises in that patient cohort²⁹ and PAH drugs are not currently recommended.³⁰ Sarcoidosis can exhibit a pulmonary vasculopathy which may benefit from pulmonary vasodilators, but must be distinguished from cardiac sarcoid and interstitial lung sarcoidosis which are unlikely to benefit.³¹ Given these issues, where severe PH is present and is disproportionate to the severity of the associated condition, discussion with a PH specialist centre may be helpful.

Conclusions

The term 'pulmonary hypertension' covers many conditions, of which only a small minority respond to PH-specific therapy. Identifying this cohort can be challenging and many patients go undiagnosed. Determining a 'pre-test' clinical level of suspicion can, however, help when interpreting subsequent investigations and determining whether or not to make an onward referral. The use of a full range of cardiopulmonary investigations can also help in determining the relative contributions of left heart and/or lung disease, the presence of which generally precludes patients from receiving PH-specific therapy (Fig 4). Many aspects of PH however remain incompletely understood – patients with clinically significant PH who do not readily fit into the standard classification may therefore warrant discussion with a specialist centre on a case-by-case basis. ■

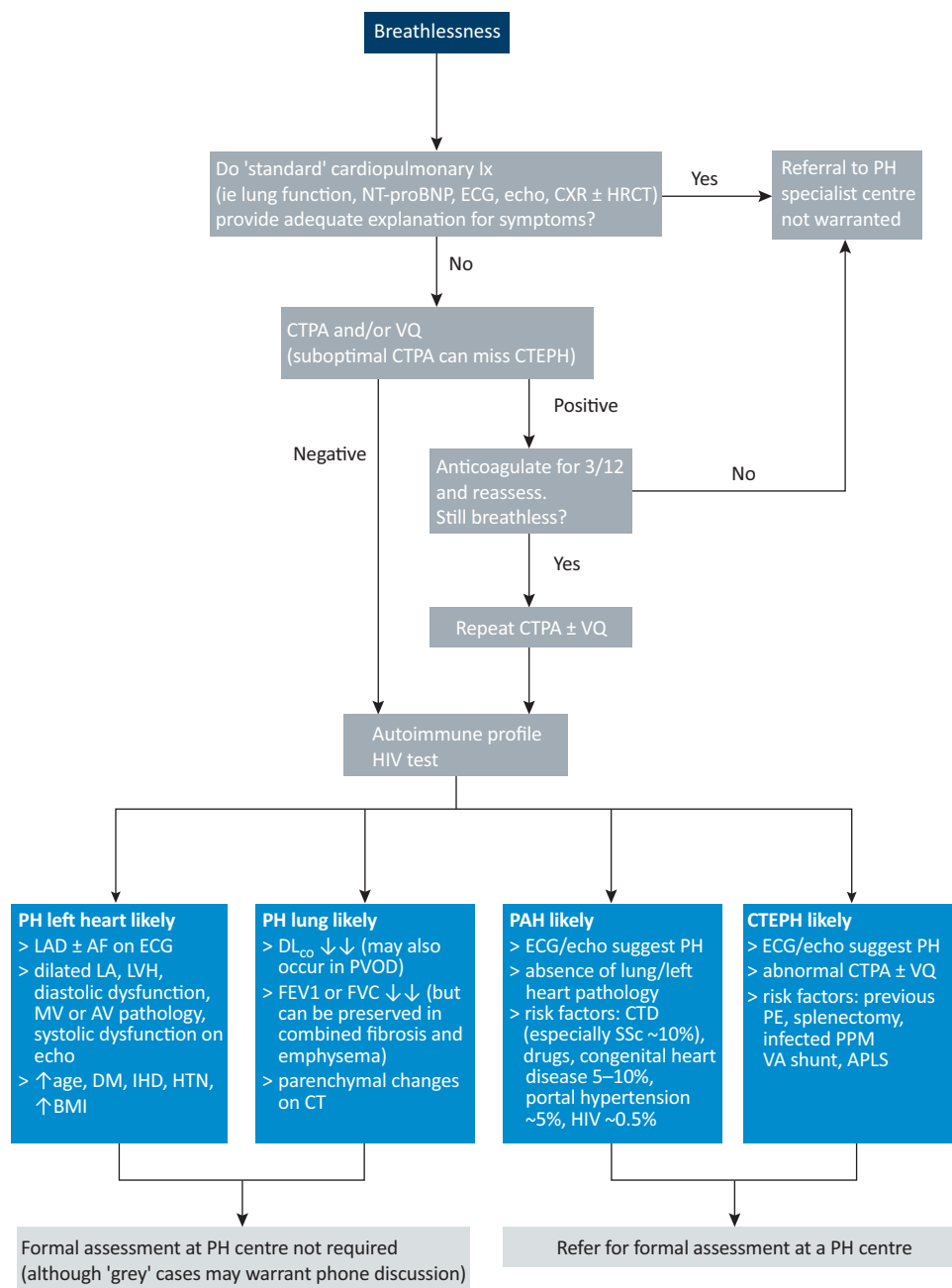
Table 2. Features that most likely indicate PH related to left heart disease.

Clinical features	Investigation findings
Age >65 years	Left axis deviation on ECG
Systemic hypertension	Dilated LA on echocardiography
Diabetes	LVH on echocardiography
Atrial fibrillation	LV diastolic dysfunction on echocardiography
Obesity	Increased E/E' on echocardiography
Ischaemic heart disease	

ECG = electrocardiogram; E/E' = ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity; LA = left atrium; LV = left ventricle; LVH = left ventricular hypertrophy.

Fig 4. Referral algorithm.

AF = atrial fibrillation; APLS = anti-phospholipid syndrome; AV = aortic valve; BMI = body mass index; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; CXR = chest radiograph; DL_{CO} = diffusing capacity of the lung for carbon monoxide; DM = diabetes mellitus; ECG = electrocardiogram; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; HIV = human immunodeficiency virus; HRCT = high resolution computed tomography; HTN = hypertension; IHD = ischemic heart disease; Ix = investigations; LA = left atrium; LAD = left anterior descending coronary artery; LVH = left ventricular hypertrophy; MV = mitral valve; NT-proBNP = N-terminal pro-brain natriuretic peptide; PE = pulmonary embolism; PH = pulmonary hypertension; PPM = pacemaker; PVOD = pulmonary veno-occlusive disease; SSC = systemic sclerosis; VA = ventriculoatrial; VQ = ventilation perfusion.



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