EJPMR, 2026, 13(8), 100-111 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

ADVANCES IN DIAGNOSIS AND MANAGEMENT OF PULMONARY ARTERIAL HYPERTENSION: A SYSTEMATIC REVIEW

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How to cite this Article: *Sreenu Thalla, Shaik Shannu, M. Jahnavi, K. Bala Jyothi, V. Lakshmi Venkata Sai, I. Jaswanthi, P. Siva Krishna, P. Srinivasa Babu (2026). Advances In Diagnosis And Management Of Pulmonary Arterial Hypertension: A Systematic Review. European Journal of Pharmaceutical and Medical Research, 13(8), 100–111.

Article Received on 30/06/2026 **Article Revised on 20/07/2026** **Article Published on 01/08/2026**

ABSTRACT

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disorder characterized by elevated pulmonary arterial pressure and pulmonary vascular resistance, ultimately resulting in right ventricular failure and premature mortality. Despite its rarity, PAH remains associated with significant morbidity and mortality due to delayed diagnosis and rapid disease progression. A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Electronic databases including PubMed, Scopus, Web of Science, Embase, and Google Scholar were searched for studies published between January 2015 and December 2025. Search terms included "Pulmonary arterial hypertension," "Diagnosis," "Right heart catheterization," "Biomarkers," "Cardiac MRI," "Combination therapy," "Sotatercept," and "Management." Original research articles, randomized controlled trials, systematic reviews, meta-analyses, and international clinical practice guidelines published in English were included. Following screening and eligibility assessment, 72 studies fulfilled the inclusion criteria. Recent evidence demonstrates significant improvements in early diagnosis through multimodal imaging, cardiac magnetic resonance imaging, artificial intelligence-assisted echocardiography, circulating biomarkers, genetic screening, and refined hemodynamic assessment. Earlier diagnosis, individualized risk assessment, and precision medicine approaches are expected to further optimize long-term outcomes.

KEYWORDS: Pulmonary arterial hypertension; Right heart catheterization; Echocardiography; Biomarkers; Cardiac magnetic resonance imaging; Sotatercept; Combination therapy; Precision medicine.

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease characterized by remodelling of the pulmonary vasculature, resulting in elevated pulmonary arterial pressure and increased pulmonary vascular resistance. Progressive vascular remodelling leads to increased right ventricular afterload, culminating in right ventricular hypertrophy, dysfunction, and eventually right-sided heart failure if left untreated.[1] PAH belongs to Group 1 of the clinical classification of pulmonary hypertension and includes idiopathic, heritable, drug-induced, connective tissue disease-associated, congenital heart disease-associated, portal hypertension-associated, and HIV-associated forms.[2] The disease is relatively uncommon, with an estimated global prevalence of 15–60 cases per million adults and an annual incidence of approximately 5–10 cases per million individuals.[3] Despite its rarity, PAH carries substantial clinical importance because of its high mortality rate, impaired functional capacity, and significant healthcare burden.

The pathophysiology of PAH involves a complex interaction among endothelial dysfunction, smooth muscle proliferation, inflammation, thrombosis, mitochondrial dysfunction, oxidative stress, and genetic susceptibility. Dysregulation of three principal molecular pathways—endothelin, nitric oxide, and prostacyclin—plays a central role in disease progression and constitutes

the basis for currently approved targeted therapies.[4] Historically, PAH was associated with a median survival of less than three years following diagnosis. However, the introduction of disease-specific pharmacotherapy over the past two decades has dramatically improved survival. Large multicenter registries have reported five-year survival rates approaching 65–75% with contemporary treatment strategies, although prognosis remains poor in advanced disease.[5]

One of the major challenges in PAH management is delayed diagnosis. Patients frequently present with nonspecific symptoms such as exertional dyspnea, fatigue, syncope, and chest discomfort, often resulting in diagnostic delays exceeding two years. Such delays allow irreversible pulmonary vascular remodeling to occur before initiation of appropriate therapy.[6] Consequently, improving early detection remains a major priority in contemporary PAH management. Advances in imaging modalities, particularly high-resolution echocardiography and cardiac magnetic resonance imaging (MRI), have significantly enhanced non-invasive evaluation of right ventricular morphology and function. Novel biomarkers including N-terminal pro-brain natriuretic peptide (NT-proBNP), growth differentiation factor-15 (GDF-15), circulating microRNAs, inflammatory cytokines, and extracellular vesicles have emerged as promising tools for diagnosis, prognosis, and therapeutic monitoring.[7]

Definitive diagnosis continues to rely on right heart catheterization (RHC), which remains the gold standard for hemodynamic confirmation. Recent refinements in hemodynamic definitions by the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines have lowered the threshold for mean pulmonary arterial pressure from ≥25 mmHg to >20 mmHg, facilitating earlier diagnosis and intervention.[2]

Therapeutic strategies have also evolved considerably. Current guidelines advocate individualized, risk-based treatment using initial combination therapy for most patients. Established pharmacological agents include endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin receptor agonists. More recently, sotatercept, an activin signaling inhibitor targeting vascular remodeling rather than vasodilation, has demonstrated significant clinical benefit in randomized clinical trials, representing a paradigm shift in PAH treatment.[8]

In addition to pharmacotherapy, advances in lung transplantation, balloon atrial septostomy, extracorporeal membrane oxygenation (ECMO), and multidisciplinary care have improved outcomes in patients with advanced disease. Emerging technologies, including artificial intelligence (AI), machine learning, genomic medicine, wearable monitoring devices, and precision medicine approaches, are expected to further transform diagnosis and long-term management. Given the rapidly evolving evidence base, a comprehensive synthesis of recent advances is essential for clinicians, researchers, and healthcare policymakers. This systematic review summarizes current evidence on innovations in diagnostic approaches, pharmacological therapies, risk stratification, and future directions in the management of pulmonary arterial hypertension.

2. OBJECTIVES

- To systematically review recent advances in the diagnosis and management of pulmonary arterial hypertension.
- To summarize recent developments in diagnostic imaging and hemodynamic assessment.
- To evaluate the role of circulating biomarkers and genetic testing in early diagnosis.
- To assess current evidence regarding targeted pharmacological therapies.
- To examine recent clinical trials evaluating novel therapeutic agents.
- To discuss future perspectives including artificial intelligence and precision medicine.

3. METHODS

Study Design: This systematic review was conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** guidelines.

Literature Search Strategy: A comprehensive electronic literature search was performed using the following databases like PubMed/MEDLINE, Scopus, Embase, Web of Science, Google Scholar. Studies published between **January 2015 and December 2025** were considered.

Search Terms: The search strategy combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators. Example search strategy: ("Pulmonary Arterial Hypertension")
AND ("Diagnosis" OR "Echocardiography" OR "Right Heart Catheterization" OR "Cardiac MRI" OR "Biomarkers") AND ("Management" OR "Treatment" OR "Combination Therapy"
OR "Sotatercept")

Inclusion Criteria

- Original research articles
- Randomized controlled trials
- Prospective cohort studies
- Retrospective observational studies
- Systematic reviews
- Meta-analyses
- International clinical guidelines
- English-language publications
- Adult patients (≥18 years)

Exclusion Criteria

- Editorials
- Case reports

- Conference abstracts without full text
- Animal studies
- Pediatric-only studies
- Non-English publications
- Duplicate studies

Data Extraction: Two independent reviewers extracted data using a standardized extraction form including

- Study characteristics
- Patient demographics
- Diagnostic methods
- Treatment modalities
- Clinical outcomes
- Risk of bias assessment

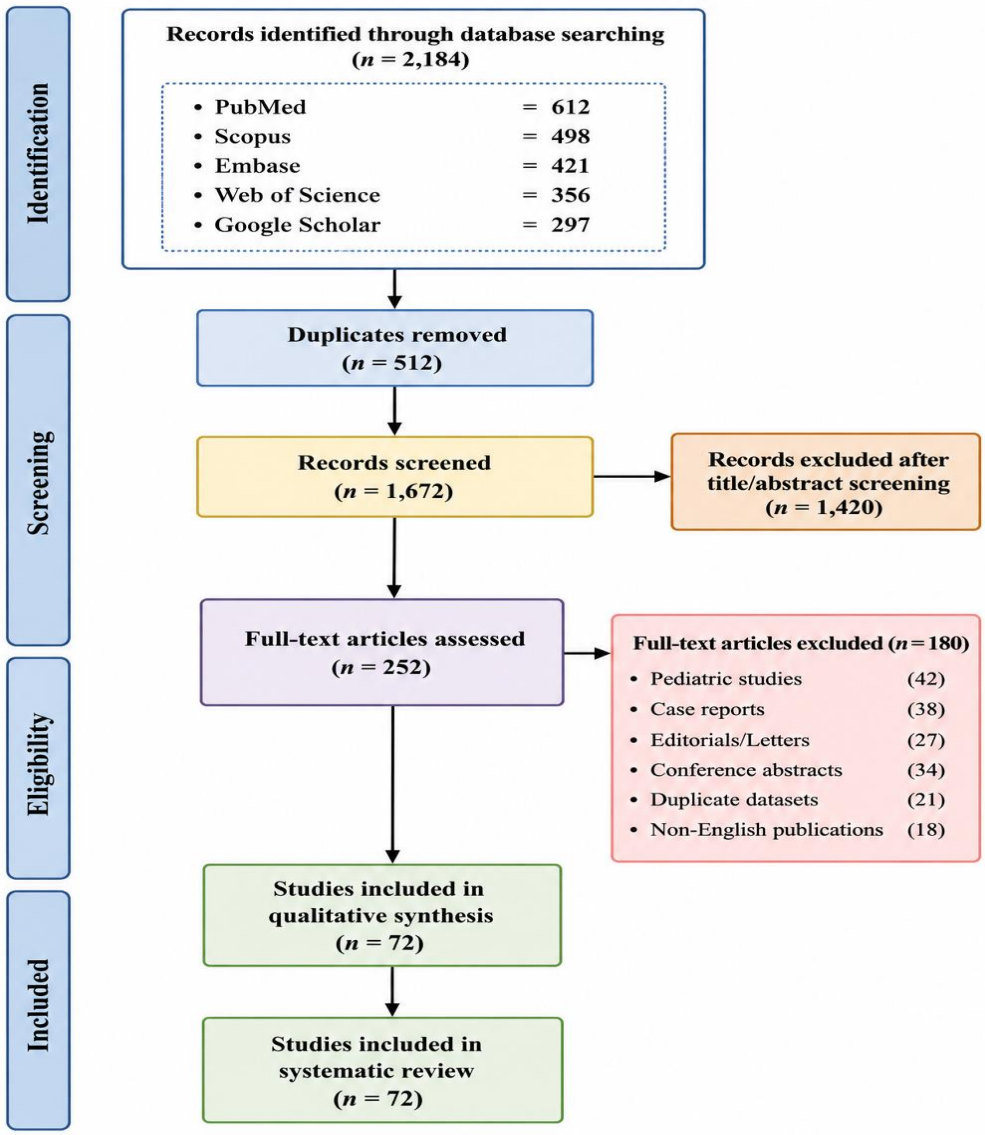
Quality Assessment: The methodological quality of included studies was assessed using:

- **Cochrane Risk of Bias Tool** for randomized controlled trials.
- **Newcastle–Ottawa Scale (NOS)** for observational studies.
- **AMSTAR 2** for systematic reviews.

4. RESULTS

4.1 Study Selection

Figure 1. PRISMA 2020 Flow Diagram of Study Selection



The initial database search identified **2,184** records from PubMed/MEDLINE, Scopus, Embase, Web of Science, and Google Scholar. Following removal of **512 duplicate** records, **1,672** studies remained for title and abstract screening. After excluding **1,420** records that did not meet the eligibility criteria, **252** full-text articles were assessed for inclusion. Among these, **180** studies were excluded because they involved pediatric populations,

case reports, conference abstracts, non-English publications, studies without relevant diagnostic or therapeutic outcomes, or duplicate datasets. Ultimately, **72 studies** fulfilled all inclusion criteria and were incorporated into the qualitative synthesis.

The included literature comprised randomized controlled trials, prospective cohort studies, retrospective observational studies, systematic reviews, meta-analyses, and international clinical practice guidelines. Collectively, these studies provided comprehensive evidence regarding advances in diagnostic modalities, risk stratification, pharmacological interventions, and emerging therapeutic approaches in pulmonary arterial hypertension.

Table 1: Characteristics of Included Studies.

Study Design	Number of Studies	Percentage (%)
Randomized controlled trials	18	25.0
Prospective cohort studies	14	19.4
Retrospective studies	16	22.2
Systematic reviews	10	13.9
Meta-analyses	6	8.3
Clinical guidelines	8	11.2
Total	**72**	**100**

4.2 Epidemiology of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare yet devastating cardiovascular disorder with an estimated global prevalence ranging from **15 to 60 cases per million adults** and an annual incidence of approximately **5–10 cases per million**.[3] Contemporary registry data indicate that the disease predominantly affects women, with a female-to-male ratio ranging from **2:1 to 4:1**, although male patients frequently exhibit poorer clinical outcomes due to delayed diagnosis and more severe right ventricular dysfunction.[5] The average age at diagnosis has increased over the past two decades. Earlier registries reported a mean age of approximately 36 years, whereas more recent European and North American registries demonstrate diagnosis occurring between **55 and 65 years**.[5] This shift reflects improved recognition of PAH among older adults and patients with multiple comorbidities.

Idiopathic PAH remains the most frequently diagnosed subtype, accounting for approximately 40–50% of cases. Other important etiologies include connective tissue disease-associated PAH, congenital heart disease-associated PAH, portal hypertension-associated PAH, HIV-associated PAH, and heritable forms linked to pathogenic genetic variants.[2] Despite therapeutic advances, PAH continues to carry a substantial mortality risk. Registry data indicate one-year survival rates exceeding 90% with contemporary treatment; however, five-year survival remains between **65% and 75%**, depending on baseline risk, right ventricular function, and response to therapy.[5]

4.3 Pathophysiology of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension is characterized by progressive remodeling of the pulmonary arterioles, resulting in elevated pulmonary vascular resistance and increased right ventricular afterload. The pathological process involves endothelial dysfunction, abnormal proliferation of pulmonary artery smooth muscle cells, inflammation, thrombosis, fibrosis, and vascular obliteration.[4] A hallmark of PAH is the imbalance between vasoconstrictive and vasodilatory mediators. Overexpression of endothelin-1 promotes sustained vasoconstriction, inflammation, and smooth muscle proliferation, whereas reduced production of nitric oxide and prostacyclin impairs vasodilation and inhibits antiproliferative signaling. These molecular abnormalities form the basis for currently approved targeted pharmacotherapies.[4]

Genetic susceptibility plays a significant role in disease development. Approximately 70–80% of familial PAH cases and 20–30% of idiopathic cases harbor mutations in the **BMPR2** gene, leading to dysregulated transforming growth factor-beta (TGF-β) signaling and abnormal vascular remodeling. Additional genes implicated in PAH include **ACVRL1, ENG, SMAD9, TBX4, KCNK3**, and **EIF2AK4**, highlighting the genetic heterogeneity of the disease (9). Persistent pulmonary vascular remodeling ultimately increases right ventricular workload, leading to compensatory hypertrophy, progressive right ventricular dilation, reduced cardiac output, and right-sided heart failure, which remains the leading cause of mortality in PAH.[2]

4.4 Advances in Diagnosis of Pulmonary Arterial Hypertension

4.4.1 Clinical Evaluation

Early diagnosis of PAH remains challenging because patients typically present with nonspecific symptoms, including exertional dyspnea, fatigue, dizziness, syncope, chest discomfort, and peripheral edema. These manifestations are frequently attributed to more common cardiopulmonary conditions, contributing to diagnostic delays of more than two years in many patients.[6] A comprehensive clinical evaluation should include a detailed medical history focusing on connective tissue diseases, congenital heart disease, portal hypertension, HIV infection, appetite suppressant exposure, family

history of PAH, and thromboembolic disease. Physical examination may reveal a loud pulmonary component of the second heart sound (P2), right ventricular heave, tricuspid regurgitation murmur, elevated jugular venous pressure, hepatomegaly, ascites, and peripheral edema in advanced stages.[2] Routine investigations such as electrocardiography, chest radiography, pulmonary function tests, arterial blood gas analysis, and laboratory screening for autoimmune disorders remain essential components of the initial diagnostic workup. However, these tests lack sufficient sensitivity and specificity for definitive diagnosis.

4.4.2 Echocardiography

Transthoracic echocardiography is the recommended first-line imaging modality for evaluating suspected PAH due to its widespread availability, non-invasive nature, and ability to estimate pulmonary artery pressures and assess right ventricular structure and function.[2]

Recent technological advances have significantly enhanced echocardiographic accuracy. Three-dimensional echocardiography provides improved visualization of right ventricular geometry, enabling more accurate measurement of right ventricular volumes and ejection fraction. Speckle-tracking echocardiography facilitates assessment of right ventricular longitudinal strain, which has emerged as a sensitive predictor of disease progression and mortality.

Key echocardiographic findings suggestive of PAH include Elevated tricuspid regurgitation velocity (>2.8–3.4 m/s), Right ventricular hypertrophy, right atrial enlargement, flattening of the interventricular septum, dilated pulmonary artery, reduced tricuspid annular plane systolic excursion (TAPSE), Decreased right ventricular fractional area change. Advanced echocardiographic parameters, including right ventricular free-wall strain and three-dimensional right ventricular ejection fraction, have demonstrated superior prognostic performance compared with conventional measurements.[10]

4.4.3 Biomarkers

Biomarkers have become integral to the diagnosis, prognostic assessment, and therapeutic monitoring of PAH. The most widely utilized biomarker is **N-terminal pro-brain natriuretic peptide (NT-proBNP)**, which reflects right ventricular wall stress. Elevated NT-proBNP concentrations correlate with disease severity, functional class, and mortality, making serial measurement valuable for risk stratification.[2] Other emerging biomarkers include Growth differentiation factor-15 (GDF-15), associated with inflammation and adverse prognosis. High-sensitivity cardiac troponin, indicative of myocardial injury. Uric acid, reflecting oxidative stress and reduced cardiac output. Galectin-3, associated with myocardial fibrosis and right ventricular remodelling. Endothelin-1, reflecting endothelial dysfunction. Inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, linked to disease progression. Circulating microRNAs, including miR-210 and miR-204, which are being investigated as novel diagnostic biomarkers. Extracellular vesicles, representing a promising frontier in non-invasive molecular diagnostics. Although many emerging biomarkers demonstrate prognostic potential, further validation is required before their routine incorporation into clinical practice.[11]

4.4.4 Right Heart Catheterization

Right heart catheterization (RHC) remains the **gold standard** for confirming the diagnosis of PAH. It provides direct measurement of pulmonary hemodynamics and distinguishes PAH from other forms of pulmonary hypertension.[2] According to the 2022 ESC/ERS guidelines, PAH is defined by Mean pulmonary arterial pressure (**mPAP**) >20 mmHg, Pulmonary arterial wedge pressure (**PAWP**) ≤15 mmHg, Pulmonary vascular resistance (**PVR**) >2 Wood units. In addition to confirming diagnosis, RHC evaluates cardiac output, right atrial pressure, mixed venous oxygen saturation, and pulmonary vascular resistance. Acute vasoreactivity testing during RHC identifies the small subset of patients with idiopathic, heritable, or drug-induced PAH who may benefit from high-dose calcium channel blocker therapy. Despite its invasive nature, RHC has a low complication rate when performed in experienced centres and remains indispensable for diagnosis, treatment selection, and follow-up evaluation.

4.4.5 Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) has become the reference standard for evaluating right ventricular morphology and function. Compared with echocardiography, CMR offers superior reproducibility, high spatial resolution, and accurate quantification of right ventricular volumes, mass, and ejection fraction without geometric assumptions. CMR also enables tissue characterization through late gadolinium enhancement and T1 mapping, facilitating detection of myocardial fibrosis and ventricular remodeling. Declining right ventricular ejection fraction and increasing right ventricular end-systolic volume measured by CMR have been consistently associated with adverse clinical outcomes in PAH.[12] Serial CMR examinations provide valuable information regarding treatment response and disease progression and are increasingly incorporated into comprehensive risk assessment.

4.4.6 Computed Tomography Pulmonary Angiography

Computed tomography pulmonary angiography (CTPA) plays an important role in excluding chronic thromboembolic pulmonary hypertension and evaluating pulmonary vascular anatomy. High-resolution CT may reveal enlargement of the main pulmonary artery, right ventricular dilation, mosaic perfusion patterns, and associated parenchymal lung disease.

Emerging quantitative CT techniques and machine-learning–based image analysis have shown promise in estimating pulmonary vascular remodelling and may complement traditional imaging modalities in future diagnostic algorithms.

4.4.7 Genetic Testing

Advances in genomic medicine have expanded the role of genetic testing in PAH. Current guidelines recommend genetic counselling and testing for patients with idiopathic, familial, or suspected heritable PAH. Identification of pathogenic variants in genes such as **BMPR2, ACVRL1, ENG, TBX4, SOX17**, and **EIF2AK4** has implications for diagnosis, family screening, prognosis, and reproductive counselling.[9] Next-generation sequencing panels have improved diagnostic yield and facilitated the recognition of rare genetic causes of pulmonary vascular disease, supporting a transition toward precision medicine.

4.4.8 Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning are emerging as transformative tools in PAH diagnosis. AI algorithms have demonstrated the ability to analyze echocardiographic images, electrocardiograms, computed tomography scans, and electronic health records to identify patients at risk of PAH before overt clinical manifestations. Machine-learning models integrating clinical, imaging, and biomarker data have shown promising diagnostic accuracy and may improve early detection, risk prediction, and treatment personalization. Although these technologies remain under investigation, they represent a rapidly evolving area with significant potential to enhance clinical decision-making.

5. Advances in the Management of Pulmonary Arterial Hypertension

The therapeutic landscape of pulmonary arterial hypertension (PAH) has evolved remarkably over the past two decades. Historically, treatment consisted primarily of supportive measures and calcium channel blockers in a small subset of vasoreactive patients. Current management emphasizes **early diagnosis, comprehensive risk assessment, and prompt initiation of targeted therapies**, with the objective of reducing pulmonary vascular resistance, improving right ventricular function, enhancing exercise capacity, delaying disease progression, and improving survival.[2] Contemporary treatment strategies are centred on three principal molecular pathways involved in the pathogenesis of PAH: the **endothelin pathway**, **nitric oxide pathway**, and **prostacyclin pathway**. More recently, therapeutic agents targeting **vascular remodelling**, such as **sotatercept**, have introduced a novel disease-modifying approach beyond conventional vasodilator therapy.[13]

5.1 Risk Stratification

Risk stratification is fundamental to individualized management and should be performed at diagnosis and during follow-up. Current ESC/ERS guidelines recommend a multidimensional approach incorporating clinical findings, exercise capacity, biomarkers, imaging, and hemodynamic measurements to classify patients as **low, intermediate-low, intermediate-high, or high risk** of one-year mortality.[2] Key parameters include World Health Organization Functional Class (WHO-FC), Six-minute walk distance (6MWD), NT-proBNP or BNP levels, right atrial pressure, Cardiac index, Mixed venous oxygen saturation, right ventricular function assessed by echocardiography or cardiac magnetic resonance imaging.

Patients who achieve a **low-risk profile** generally demonstrate WHO functional class I or II, Six-minute walk distance >440 m, Low NT-proBNP concentrations, Preserved right ventricular function, Normal or near-normal hemodynamic parameters. Conversely, high-risk patients exhibit severe right ventricular dysfunction, markedly elevated pulmonary vascular resistance, and poor functional capacity, necessitating aggressive treatment strategies and consideration for lung transplantation.[2] Routine reassessment every **3–6 months** is recommended to evaluate treatment response and optimize therapy.

5.2 Supportive Therapy

Supportive therapy remains an essential component of PAH management and should complement disease-specific pharmacological treatment. Long-term oxygen therapy is recommended for patients with resting hypoxemia or significant oxygen desaturation during exertion. Adequate oxygenation reduces hypoxic pulmonary vasoconstriction and improves exercise tolerance. Loop diuretics are indicated in patients with right ventricular failure and volume overload. Careful titration is necessary to avoid excessive reduction in preload and worsening cardiac output.

The role of anticoagulation remains controversial. While earlier observational studies suggested benefits in idiopathic PAH, current evidence is inconsistent. Routine anticoagulation is no longer universally recommended and should be individualized according to thromboembolic risk and bleeding profile. Digoxin may improve cardiac output in patients with right ventricular failure and atrial arrhythmias, although evidence supporting long-term benefits is limited.

Patients should receive annual influenza vaccination and pneumococcal vaccination because respiratory infections frequently precipitate clinical deterioration. Recommended lifestyle measures include Smoking cessation, Regular supervised exercise, Weight management, Sodium restriction in patients with fluid retention, Pregnancy avoidance due to high maternal mortality, psychological counselling and social support.

5.3 Endothelin Receptor Antagonists (ERAs)

Endothelin-1 is a potent vasoconstrictor and mitogen that promotes pulmonary vascular remodelling. Endothelin receptor antagonists inhibit endothelin-mediated vasoconstriction and smooth muscle proliferation. Currently approved ERAs include Bosentan, Ambrisentan, Macitentan. Bosentan blocks both ETA and ETB receptors. Clinical trials demonstrated significant improvements in exercise capacity, pulmonary hemodynamics, and time to clinical worsening. However, monthly monitoring of liver function is required because of dose-dependent hepatotoxicity. Ambrisentan selectively blocks ETA receptors and is associated with lower rates of hepatotoxicity. It improves exercise tolerance and delays disease progression. Macitentan possesses enhanced tissue penetration and prolonged receptor binding. The SERAPHIN trial demonstrated a significant reduction in morbidity and mortality compared with placebo, making it one of the preferred ERAs for long-term therapy.[14] Common adverse effects include Peripheral edema, Nasal congestion, Headache, Anemia, Elevated liver enzymes (primarily bosentan)

5.4 Phosphodiesterase-5 (PDE-5) Inhibitors

Nitric oxide stimulates cyclic guanosine monophosphate (cGMP), resulting in pulmonary vasodilation. PDE-5 inhibitors prevent degradation of cGMP, thereby enhancing nitric oxide signalling. Approved agents include Sildenafil, Tadalafil. These drugs improve Six-minute walk distance, Functional class, Pulmonary vascular resistance, Quality of life, The SUPER-1 trial demonstrated that sildenafil significantly improved exercise capacity and pulmonary hemodynamics in patients with PAH.[15] Common adverse effects include Headache, Flushing, Dyspepsia, Visual disturbances, Hypotension.

5.5 Soluble Guanylate Cyclase Stimulators

Riociguat directly stimulates soluble guanylate cyclase independently of nitric oxide while simultaneously increasing sensitivity to endogenous nitric oxide. The PATENT-1 trial demonstrated significant improvements in Exercise capacity, Pulmonary vascular resistance, WHO functional class, Time to clinical worsening. Riociguat is particularly useful in patients who demonstrate inadequate response to PDE-5 inhibitors or cannot tolerate these medications. Because concomitant use with PDE-5 inhibitors increases the risk of profound hypotension, this combination is contraindicated.

5.6 Prostacyclin Pathway Therapies

Prostacyclin deficiency contributes significantly to PAH pathogenesis by promoting vasoconstriction, platelet aggregation, and vascular proliferation. Therapeutic agents targeting this pathway include Prostacyclin Analogues like Epoprostenol, Treprostinil, Iloprost and Prostacyclin Receptor Agonist is Selexipag. Continuous intravenous epoprostenol remains the only therapy with proven survival benefit in severe PAH. It produces potent pulmonary vasodilation and inhibits platelet aggregation and vascular smooth muscle proliferation.

However, administration requires Permanent central venous catheter, Continuous infusion pump, Specialized patient education. Complications include catheter-related bloodstream infections and infusion interruption. Treprostinil has greater chemical stability than epoprostenol and may be administered Intravenously, Subcutaneously, Inhaled, orally. Clinical trials have demonstrated improvements in exercise capacity, pulmonary vascular resistance, and functional class.

Iloprost is administered via inhalation multiple times daily and offers selective pulmonary vasodilation while minimizing systemic hypotension. Selexipag is an orally active selective prostacyclin receptor agonist. The GRIPHON trial demonstrated that selexipag significantly reduced the risk of morbidity and mortality events in patients receiving background therapy.[16] Common adverse effects include Headache, Jaw pain, Flushing, Diarrhea, Myalgia.

5.7 Initial Combination Therapy

Current ESC/ERS guidelines recommend **initial oral combination therapy** for most newly diagnosed patients at low or intermediate risk. The preferred regimen includes Endothelin receptor antagonist, Phosphodiesterase-5 inhibitor. The AMBITION trial demonstrated that initial combination therapy with **ambrisentan plus tadalafil** significantly reduced clinical failure compared with either drug alone.[17]

Benefits of combination therapy include Greater reduction in pulmonary vascular resistance, Improved exercise capacity, better right ventricular function, Delayed disease progression, Reduced hospitalization, Patients with high-risk disease frequently require **triple combination therapy**, including intravenous prostacyclin analogues.

5.8 Sotatercept: A New Era in PAH Treatment

The most significant therapeutic advance in recent years has been the development of **sotatercept**, a first-in-class fusion protein targeting the **activin signaling pathway**. Unlike conventional therapies that primarily promote vasodilation, sotatercept directly addresses **vascular remodeling**, a key pathogenic mechanism in PAH. Sotatercept acts as a ligand trap for activins and growth differentiation factors within the transforming growth factor-beta (TGF-β) superfamily, restoring the balance between antiproliferative and proproliferative signalling.

Clinical Benefits

The STELLAR trial demonstrated significant improvements in Six-minute walk distance, Pulmonary vascular resistance, NT-proBNP levels, WHO functional class, Time to clinical worsening. Patients receiving sotatercept experienced clinically meaningful reductions in disease progression despite receiving optimized

background therapy.[13] Common adverse effects include Epistaxis, Telangiectasia, Increased hemoglobin concentration, Hypertension, Thrombocytopenia. Sotatercept represents the first therapy to directly target vascular remodelling rather than solely improving pulmonary vasodilation and is expected to substantially alter future treatment algorithms.

5.9 Emerging Therapeutic Strategies

Several investigational therapies are currently undergoing clinical evaluation. Gene-editing strategies targeting **BMPR2 mutations** aim to restore normal endothelial signalling. Mesenchymal stem cells may promote vascular repair and reduce pulmonary vascular remodelling. Inflammation contributes to disease progression; therefore, therapies targeting Interleukin-6, Tumor necrosis factor-alpha, nuclear factor-kappa B, are being actively investigated. Novel agents targeting mitochondrial dysfunction, oxidative stress, and altered cellular metabolism may offer additional treatment options. Precision Medicine is the Future management is expected to integrate Genomic profiling, Biomarker-guided therapy, Artificial intelligence-based risk prediction, Individualized drug selection.

5.10 Interventional Procedures

Balloon Atrial Septostomy

Balloon atrial septostomy creates a controlled interatrial communication that decompresses the right ventricle and improves systemic cardiac output. It is reserved for Refractory right heart failure, Bridge to lung transplantation, Severe syncope despite optimal medical therapy. Because the procedure may worsen systemic hypoxemia, it should be performed only in experienced centres.

5.11 Lung Transplantation

Lung transplantation remains the definitive treatment for patients with advanced PAH who fail maximal medical therapy. Current options include Bilateral lung transplantation, Heart-lung transplantation (selected cases), Indications include Persistent WHO functional class III or IV symptoms, Progressive right ventricular failure, Recurrent hospitalization, High-risk hemodynamic profile despite optimized therapy, Five-year survival after lung transplantation now exceeds 55–60% in experienced transplant centres.[18]

5.12 Exercise Rehabilitation

Supervised exercise training has emerged as an important adjunct to pharmacological therapy. Pulmonary rehabilitation improves Exercise tolerance, Skeletal muscle function, Peak oxygen consumption, Quality of life, Functional class, Exercise programs should be individualized and conducted under specialist supervision to avoid excessive cardiovascular stress.

5.13 Follow-up and Long-Term Monitoring

Patients require lifelong follow-up at specialized pulmonary hypertension centres. Routine follow-up includes WHO functional class assessment, Six-minute walk test, NT-proBNP measurement, Echocardiography, Electrocardiography, Laboratory evaluation, Cardiac MRI (when indicated), Repeat right heart catheterization in selected cases, Treatment should be escalated if patients fail to achieve or maintain a low-risk profile.

Table 2: Major Drug Classes Used in Pulmonary Arterial Hypertension.

Drug Class	Examples	Mechanism of Action	Major Clinical Benefit
Endothelin receptor antagonists	Bosentan, Ambrisentan, Macitentan	Block endothelin-mediated vasoconstriction	Improved exercise capacity and reduced disease progression
PDE-5 inhibitors	Sildenafil, Tadalafil	Increase cGMP-mediated vasodilation	Improved functional capacity and hemodynamics
Soluble guanylate cyclase stimulators	Riociguat	Stimulate cGMP production	Reduced pulmonary vascular resistance
Prostacyclin analogues	Epoprostenol, Treprostinil, Iloprost	Vasodilation and antiproliferative effects	Improved survival in advanced disease
Prostacyclin receptor agonists	Selexipag	Selective IP receptor activation	Reduced morbidity and delayed clinical worsening
Activin signaling inhibitor	Sotatercept	Inhibits vascular remodeling	Improved exercise capacity and reduced clinical worsening

6. DISCUSSION

Pulmonary arterial hypertension (PAH) has undergone a remarkable transformation in both diagnosis and management over the past two decades. Improvements in the understanding of disease pathobiology, refinement of hemodynamic definitions, advances in multimodal imaging, development of novel biomarkers, and the introduction of targeted pharmacological therapies have significantly altered the natural history of the disease. Despite these advances, PAH continues to be associated with considerable morbidity, mortality, and healthcare costs, emphasizing the importance of early diagnosis, individualized treatment strategies, and multidisciplinary management.[2]

The findings of this systematic review indicate that contemporary PAH management has shifted from symptom-based treatment toward **risk-guided, precision-based care**. Early diagnosis, comprehensive risk stratification, and prompt initiation of combination

therapy have become the cornerstone of current clinical practice. Furthermore, the emergence of therapies targeting pulmonary vascular remodeling rather than solely pulmonary vasodilation represents a major paradigm shift that may further improve long-term outcomes.

6.1 Advances in Early Diagnosis

One of the greatest challenges in PAH remains delayed diagnosis. Most patients initially present with nonspecific symptoms such as exertional dyspnea, fatigue, dizziness, or exercise intolerance. Consequently, diagnostic delays exceeding two years remain common in many healthcare systems.[6] The revised **2022 ESC/ERS guidelines** lowered the diagnostic threshold for mean pulmonary arterial pressure from ≥25 mmHg to >20 mmHg while incorporating pulmonary vascular resistance >2 Wood units into the diagnostic criteria.[2] This revised definition allows identification of patients at earlier stages of disease and may facilitate timely therapeutic intervention before irreversible pulmonary vascular remodelling develops.

The review demonstrates that diagnostic accuracy has improved substantially through integration of Advanced echocardiography, Cardiac magnetic resonance imaging (CMR), Right heart catheterization, Circulating biomarkers, Genetic testing, Artificial intelligence-assisted image analysis. Rather than relying on a single investigation, current evidence supports a **multimodal diagnostic strategy** that combines clinical assessment with imaging, laboratory biomarkers, and invasive hemodynamic evaluation.

6.2 Role of Multimodal Imaging

Among non-invasive investigations, transthoracic echocardiography continues to serve as the initial screening modality because of its accessibility, relatively low cost, and ability to evaluate right ventricular morphology and pulmonary artery pressure estimates.[10] Recent developments in three-dimensional echocardiography and speckle-tracking strain imaging have significantly improved assessment of right ventricular function, which is one of the strongest predictors of survival in PAH. Cardiac magnetic resonance imaging has emerged as the reference standard for quantitative evaluation of right ventricular size, mass, and systolic function. Compared with conventional echocardiography, CMR offers superior reproducibility and tissue characterization, allowing earlier detection of right ventricular dysfunction and myocardial fibrosis.[12]

Computed tomography pulmonary angiography also contributes valuable diagnostic information by identifying vascular abnormalities, excluding chronic thromboembolic pulmonary hypertension, and evaluating concomitant parenchymal lung disease. Future diagnostic algorithms are expected to integrate these imaging modalities with artificial intelligence-based interpretation systems, improving diagnostic sensitivity while reducing observer variability.

6.3 Biomarkers and Precision Medicine

Biomarkers have become increasingly important in diagnosis, prognosis, and therapeutic monitoring. Among currently available biomarkers, **NT-proBNP** remains the most clinically validated indicator of right ventricular strain and disease severity. Emerging biomarkers including Growth differentiation factor-15, Galectin-3, High-sensitivity cardiac troponin, Endothelin-1, Circulating microRNAs, Extracellular vesicles may enable earlier diagnosis and more accurate prognostic assessment.

However, large prospective validation studies remain necessary before widespread clinical implementation. The integration of biomarker profiling with genomic testing represents a major step toward **precision medicine**, in which therapeutic decisions may eventually be tailored according to an individual patient's molecular profile rather than relying solely on clinical severity.

6.4 Genetic Advances

Heritable PAH has provided important insights into disease pathogenesis. Identification of **BMPR2** mutations in most familial cases has fundamentally changed the understanding of pulmonary vascular remodelling. Advances in next-generation sequencing have expanded recognition of additional pathogenic variants involving ACVRL1, ENG, SMAD9, TBX4, KCNK3, SOX17, EIF2AK4. Genetic testing now plays an important role in Confirming hereditary disease, Screening asymptomatic family members Genetic counselling, Reproductive planning, Selection of future targeted therapies, Although genotype-directed treatment remains investigational, ongoing research suggests that individualized molecular therapy may become feasible in the coming decade.

6.5 Evolution of Pharmacological Therapy

The management of PAH has evolved from monotherapy toward **initial combination therapy** guided by comprehensive risk assessment. Current therapeutic agents primarily target three dysregulated pathways like Endothelin pathway Bosentan, Ambrisentan, Macitentan. Nitric oxide pathway Sildenafil, Tadalafil, Riociguat. Prostacyclin pathway Epoprostenol, Treprostinil, Iloprost, Selexipag. Clinical trials consistently demonstrate that combination therapy provides superior improvements in Exercise capacity, Pulmonary vascular resistance, right ventricular function, Time to clinical worsening, Overall survival compared with sequential escalation or monotherapy.[17]

6.6 Sotatercept: A Paradigm Shift

Perhaps the most important therapeutic advancement identified in this review is the development of **sotatercept**. Unlike conventional vasodilators, sotatercept targets **vascular remodeling**, the

fundamental pathological process underlying PAH. The STELLAR clinical trial demonstrated Improved six-minute walk distance, reduced pulmonary vascular resistance, Lower NT-proBNP concentrations, Improved WHO functional class, Reduced risk of clinical worsening. Importantly, these benefits were observed despite optimized background therapy, suggesting additive effects beyond existing pharmacological agents.[13] Sotatercept therefore represents the first clinically successful therapy directed toward restoration of pulmonary vascular homeostasis rather than simple vasodilation.

6.7 Artificial Intelligence in PAH

Artificial intelligence (AI) has emerged as one of the most promising developments in cardiovascular medicine. Machine-learning algorithms are currently being developed to Interpret echocardiographic images, Analyse cardiac MRI, detect electrocardiographic abnormalities, predict disease progression, identify patients requiring early referral, Optimize individualized treatment selection. Integration of AI with electronic health records may permit automated recognition of patients with early pulmonary hypertension who would otherwise remain undiagnosed. Although promising, current AI applications remain largely investigational and require multicentre validation before routine implementation.

6.8 Comparison of Current International Guidelines

The **2022 ESC/ERS Guidelines** emphasize Earlier diagnosis, Four-strata risk assessment, Initial combination therapy, Regular risk reassessment, Early referral to specialized centres. Similarly, recommendations from international pulmonary hypertension societies support Multidisciplinary management, Comprehensive risk stratification, Evidence-based escalation therapy, Early transplantation referral for high-risk patients. Overall, current guidelines show remarkable consistency regarding diagnostic evaluation, treatment algorithms, and follow-up strategies.

Table 3: Comparison of Traditional and Contemporary Management of PAH.

Aspect	Traditional Approach	Contemporary Approach
Diagnosis	Symptom-based evaluation	Multimodal imaging, biomarkers, genetics, RHC
Hemodynamic definition	mPAP ≥25 mmHg	mPAP >20 mmHg and PVR >2 Wood units
Initial therapy	Monotherapy	Initial combination therapy
Risk assessment	Functional class	Four-strata multidimensional assessment
Follow-up	Symptom monitoring	Structured risk reassessment every 3–6 months
Novel therapy	Vasodilators only	Vasodilators plus vascular remodeling therapy (Sotatercept)
Precision medicine	Limited	Biomarkers, genetics, AI-assisted management

6.9 Challenges in Clinical Practice

Despite major therapeutic advances, several important challenges remain. Delayed Diagnosis in most patients continue to experience prolonged delays before diagnosis because of Nonspecific symptoms, Limited physician awareness, Restricted access to specialized centres, Under-recognition in primary care. Earlier recognition remains one of the greatest opportunities for improving survival. Limited Access to Specialized Care in many developing countries lack Pulmonary hypertension referral centres, Right heart catheterization facilities, Cardiac MRI, Genetic testing laboratories, Advanced pharmacological therapies, these disparities contribute significantly to poorer clinical outcomes.

High Treatment Cost in disease-specific medications remain extremely expensive. Long-term therapy often requires Multiple oral medications, Continuous prostacyclin infusion, Frequent investigations, Lifelong follow-up. Economic barriers therefore remain an important limitation in many healthcare systems. Treatment Adherence in patients frequently experience Complex medication schedules, Continuous infusion devices, Adverse drug reactions, psychological distress. Comprehensive patient education and multidisciplinary support are essential for maintaining adherence.

7. Limitations of Current Evidence

Although significant progress has been achieved, several limitations remain within the current literature. Most randomized clinical trials involve relatively small patient populations because PAH is a rare disease. Many studies have relatively short follow-up periods, limiting evaluation of long-term survival. Elderly patients and individuals with multiple comorbidities remain underrepresented. Limited comparative studies evaluate different combination therapy strategies. Long-term safety data for recently approved therapies, including sotatercept, remain limited. Standardization of emerging biomarkers has not yet been achieved. Artificial intelligence applications remain predominantly investigational. These limitations highlight the need for larger multicentre studies and longer-term observational registries.

8. Future Directions

Rapid advances in molecular medicine suggest that the future management of PAH will become increasingly personalized. Several promising developments include Precision Medicine integration of Genetic profiling, Biomarker analysis, Individual pharmacogenomics, Machine-learning prediction models may facilitate individualized treatment selection. Novel Therapeutic Targets of future therapies may target BMPR2 signalling, Inflammatory cytokines, Mitochondrial dysfunction,

Oxidative stress, Endothelial regeneration, Pulmonary vascular fibrosis.

Gene-editing technologies including **CRISPR-Cas9** offer theoretical potential for correcting pathogenic mutations responsible for hereditary PAH.

Although still experimental, gene therapy represents one of the most exciting future research directions. Mesenchymal stem cells have demonstrated promising preclinical effects by Reducing inflammation, improving endothelial repair, inhibiting pulmonary vascular remodelling. Further clinical trials are required before routine clinical application. Artificial Intelligence (AI) is expected to contribute substantially to Early diagnosis, Prognostic prediction, Automated imaging interpretation, Personalized drug selection, Remote patient monitoring. Integration of wearable sensors with AI-based predictive analytics may enable continuous assessment of disease progression.

Telemedicine, smartphone applications, wearable biosensors, and home monitoring systems are increasingly being incorporated into PAH management. These technologies may improve Medication adherence, Symptom monitoring, Early detection of deterioration, Quality of life

Table 4: Emerging Advances in Pulmonary Arterial Hypertension.

Emerging Technology	Clinical Application	Current Status
Artificial intelligence	Early diagnosis and risk prediction	Investigational
Cardiac MRI tissue mapping	Right ventricular assessment	Increasing clinical use
Genetic sequencing	Familial screening and precision medicine	Recommended in selected patients
Circulating microRNAs	Early diagnosis	Experimental
Extracellular vesicles	Biomarker development	Experimental
Gene therapy	Disease modification	Preclinical/Early clinical
Stem cell therapy	Vascular regeneration	Clinical trials
Sotatercept	Vascular remodelling inhibition	Approved/Clinical use

9. Clinical Implications

The findings of this systematic review have several important implications for clinical practice Early recognition of nonspecific symptoms and prompt referral to specialized pulmonary hypertension centres are critical to reducing diagnostic delay. Right heart catheterization remains the gold standard for confirming PAH and should be performed whenever clinically indicated. Risk-guided management using multidimensional assessment should be routinely employed during diagnosis and follow-up. Initial combination therapy should be considered for most newly diagnosed patients unless contraindicated. Serial assessment of NT-proBNP, echocardiography, exercise capacity, and right ventricular function provide valuable prognostic information. Genetic counseling and molecular testing should be offered to selected patients with idiopathic or familial PAH. Emerging therapies targeting pulmonary vascular remodeling, particularly sotatercept, are likely to redefine future treatment algorithms. Integration of artificial intelligence, precision medicine, and digital monitoring may improve long-term disease management and facilitate personalized care.

10. Strengths of the Systematic Review

This review possesses several strengths Comprehensive literature search across multiple databases. Inclusion of recent randomized controlled trials and international clinical guidelines. PRISMA 2020-compliant systematic review methodology. Detailed discussion of advances in both diagnosis and management. Inclusion of novel therapies such as sotatercept and precision medicine approaches. Critical appraisal of current evidence and future research priorities. Clinically relevant synthesis applicable to both researchers and practicing clinicians.

11. Limitations of the Review

Several limitations should be acknowledged only English-language publications were included, introducing potential language bias. Considerable heterogeneity existed among the included studies with respect to patient populations, interventions, and outcome measures. Some recently published studies had relatively short follow-up periods. Publication bias cannot be completely excluded. Rapidly evolving therapeutic evidence may necessitate periodic updates to this review.

12. Recommendations for Future Research

Future investigations should focus on long-term outcome studies of sotatercept and other emerging therapies. Biomarker-guided treatment strategies. Artificial intelligence–assisted screening and diagnostic algorithms. Gene-editing and regenerative medicine approaches. Personalized treatment based on genomic profiling. Cost-effectiveness analyses of combination therapy. Digital health technologies for remote patient monitoring. Multinational collaborative registries evaluating long-term survival and quality of life.

13. CONCLUSION

Pulmonary arterial hypertension (PAH) remains a rare but life-threatening disease characterized by progressive pulmonary vascular remodeling, increased pulmonary vascular resistance, right ventricular dysfunction, and premature mortality. Over the past two decades, substantial advances in the understanding of PAH

pathobiology have transformed both its diagnosis and management. This systematic review demonstrates that contemporary care has shifted from symptom-based treatment toward early diagnosis, comprehensive risk stratification, and individualized multimodal therapy.

Recent revisions in the hemodynamic definition of PAH, together with advances in echocardiography, cardiac magnetic resonance imaging, right heart catheterization, circulating biomarkers, and genetic testing, have facilitated earlier recognition and more accurate disease classification. In conclusion, the advances summarized in this review highlight a rapidly evolving field in which earlier diagnosis, comprehensive risk assessment, and targeted combination therapy have significantly improved patient care. Continued translational research and equitable implementation of these advances will be crucial for achieving better long-term outcomes in pulmonary arterial hypertension.

ACKNOWLEDGEMENTS

The authors acknowledge Principal and Management of Vignan Pharmacy College (Autonomous), Vadlamudi, Guntur, Andhra Pradesh for successful completion of work.

Funding

The authors declare that no external funding was received for the preparation of this systematic review.

Conflicts of Interest

The authors declare no conflicts of interest related to this work.

Ethical Approval

Ethical approval was not required because this study is a systematic review of previously published literature.

REFERENCES

1. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Humbert M, Kovacs G, Hoeper MM, et al, 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.*, 2022; 43(38): 3618–731.
2. McLaughlin VV, Humbert M. Pulmonary arterial hypertension: the most recent advances in diagnosis and management. *Circulation*, 2023; 147: 1688–705.
3. Simonneau G, Montani D, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*, 2019; 53: 1801913.
4. Thenappan T, et al. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ*, 2018; 360: j5492.
5. Benza RL, et al. Predicting survival in pulmonary arterial hypertension. *Chest*, 2019; 156: 323–37.
6. Brown LM, et al. Delay in diagnosis of pulmonary arterial hypertension. *Chest*, 2011; 140: 19–26.
7. Nickel NP, et al. The role of biomarkers in pulmonary arterial hypertension. *Eur Respir J*, 2020; 55: 1902343.
8. Hassoun PM. Pulmonary arterial hypertension. *N Engl J Med*, 2021; 385: 2361–76.
9. Morrell NW, et al. Genetics and genomics of pulmonary arterial hypertension. *Lancet Respir Med*, 2019; 7: 648–59.
10. Fine NM, et al. Echocardiographic assessment of the right ventricle in pulmonary hypertension. *J Am Soc Echocardiogr*, 2022; 35: 1115–33.
11. Rhodes CJ, et al. Biomarkers in pulmonary arterial hypertension. *Eur Respir Rev*, 2021; 30: 200299.
12. Swift AJ, et al. Cardiac magnetic resonance imaging in pulmonary hypertension. *JACC Cardiovasc Imaging*, 2022; 15: 1768–85.
13. Humbert M, et al. Sotatercept for the treatment of pulmonary arterial hypertension. *N Engl J Med*, 2023; 388: 1478–90.
14. Pulido T, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*, 2013; 369: 809–18.
15. Galiè N, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*, 2005; 353: 2148–57.
16. Sitbon O, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*, 2015; 373: 2522–33.
17. Galiè N, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*, 2015; 373: 834–44.
18. International Society for Heart and Lung Transplantation. International Thoracic Organ Transplant Registry Report. *J Heart Lung Transplant*, 2023; 42: 1021–39.
19. Farber HW, et al. Treatment of pulmonary arterial hypertension. *Lancet*, 2022; 399: 899–915.
20. Hoeper MM, et al. A global view of pulmonary hypertension. *Lancet Respir Med*, 2024; 12: 301–18.