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Review Article

Prognostic implications of pulmonary hypertension in heart failure preserved and reduced ejection fraction

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ABSTRACT

Pulmonary hypertension (PH) attributable to left heart disease (PH associated with left heart disease, PH-LHD) is the most common type of PH. PH-LHD is an important indicator of elevated morbidity and mortality in individuals with heart failure, both heart failure with preserved and reduced ejection fraction despite receive adequate therapy.
Literature was sourced from major scientific databases and studies relevant to symptoms, examinations, management, and prognostic implications of PH-LHD. Pathophysiologically, PH-LHD is a gradual process that begins with increased left-heart pressure (postcapillary component), which triggers a series of biological changes in the pulmonary vasculature (precapillary component). This process ultimately places an excessive burden on the right ventricle, resulting in right ventricular dysfunction and failure, which are the main determinants of prognosis. Symptoms of PH-LHD are usually characterized by disproportionate dyspnea that is not consistent with left ventricular ejection fraction and other comorbidities. Echocardiography can noninvasively assess the probability of pulmonary hypertension in heart failure patients. A definitive diagnosis of PH-LHD requires confirmation through right heart catheterization. The most important prognostic factors are not only determined by the degree of hemodynamic severity, but also depend heavily on the degree of right ventricular dysfunction and the status of right ventricle–pulmonary artery coupling. Management of PH-LHD is through optimization of basic Guideline-Directed Medical Therapy (GDMT) to reduce mortality and morbidity.

1. Introduction

Heart failure (HF) continues to be a global health issue and is among the primary reasons of hospitalization globally. Pulmonary hypertension (PH) is a prevalent and critical prognostic consequence of heart failure. A current meta-analysis and systematic review assessed the overall prevalence of pulmonary hypertension in heart failure patients to be approximately 46.6%, increasing to 62.5% in studies employing right heart catheterization (RHC) as the definitive diagnostic method for PH.[1]

The occurrence of pulmonary hypertension in patients with left heart failure (pulmonary hypertension owing to left heart disease, PH-LHD; Group 2) is a significant consequence. PH-LHD is a primary factor contributing to adverse outcomes, correlating with elevated in-hospital mortality and a heightened likelihood of recurrent hospitalizations.[2] The existence of pulmonary hypertension indicates a progression to a more advanced phase of cardiopulmonary disease, wherein elevated pulmonary pressure imposes an increasing burden on the right ventricle (RV).[3]

The 2022 guidelines from the European Respiratory Society (ERS) and European Society of Cardiology (ESC) the revised the hemodynamic criteria for pulmonary hypertension (PH). Presently, PH is universally characterized by a mean pulmonary arterial pressure (mPAP) over 20 mmHg at rest.[4] PH-LHD is categorized as postcapillary pulmonary hypertension, characterized by a mPAP over 20 mmHg and a pulmonary artery wedge pressure (PAWP) beyond 15 mmHg.[5]

The significant prevalence of PH problems in heart failure patients underscores the necessity for appropriate therapy of heart failure.[6] Despite robust evidence endorsing the four pillars of heart failure therapy, known as foundational quadruple guideline-directed medical therapy (GDMT), for effectively mitigating heart failure complications and decreasing rehospitalization rates, registry data indicate that fewer than 1% of patients with heart failure with reduced ejection fraction (HFrEF) receive the optimal dosage of all four drug classes.[6] Hospitalization for acute decompensated heart failure (ADHF) or other forms of acute heart failure might elevate morbidity and death rates, while also indicating inadequate heart failure management.[4] Patients with HF caused by isolated systolic hypertension (ISH) have increased clinical worse outcomes, including cardiovascular mortality, length of stay, and rehospitalization.[7]

This literature review examines the likelihood of pulmonary hypertension in left heart failure, considering patient characteristics, physical examinations, and basic diagnostic procedures. Thus, if a high probability is found, GDMT-appropriate therapy can be initiated immediately intra-hospital, avoiding inappropriate and potentially harmful therapy.[8]

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Table 1. Definition and classification of Heart Failure.[6]

Categories	Criteria 1	Criteria 2 (LVEF)	Criteria 3
HFrEF	Symptoms ± signs of heart failure	LVEF ≤ 40%	–
HFmrEF	Symptoms ± signs of heart failure[a]	LVEF 41–49%	–
HFpEF	Symptoms ± signs of heart failure[a]	LVEF ≥ 50%	Objective evidence of anatomical and/or functional cardiac abnormalities indicative of left ventricular diastolic dysfunction or heightened LV filling pressure, including high natriuretic peptides.

2. Heart Failure induce Pulmonary Hypertension

Heart failure is a clinical syndrome defined by particular symptoms (e.g., dyspnea, fatigue) that may be associated with clinical signs (such as elevated jugular venous pressure, pulmonary rales, and peripheral edema), resulting from structural and/or functional heart abnormalities, leading to diminished cardiac output and/or heightened intracardiac filling pressure.[9] The categorization of heart failure, as per the universal definition based on left ventricular ejection fraction (LVEF), comprises: Heart Failure with Preserved Ejection Fraction (HFpEF) (LVEF ≥50%), Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF) (LVEF 40–49%), and Heart Failure with Reduced Ejection Fraction (HFrEF) (LVEF <40%) accompanied by heart failure symptoms or signs.[10]

In patients with left heart failure accompanied with PH, symptoms like exertional dyspnea and physical indications such as peripheral edema frequently coincide with indicators of the underlying left heart disease, rendering them generally generic. Initial suspicion of PH-LHD typically emerges when there is an incongruity between the severity of symptoms and left heart function measures.[11]

The primary clinical manifestation of pulmonary hypertension is "disproportionate dyspnea".[11] The phrase denotes a level of dyspnea or exercise intolerance that seems more pronounced than the indicators of LVEF, volume status, or the extent of concurrent pulmonary conditions (e.g., COPD).[12] These "disproportionate" symptoms may elevate the likelihood of a substantial augmentation in the pulmonary vascular component. This scenario indicates a suspicion of elevated pulmonary vascular resistance (PVR) rather than merely increased pulmonary artery wedge pressure (PAWP), which may be exacerbating the patient's symptoms.[11]

Additional clinical manifestations indicating the potential for PH-LHD include:[11]

- Refractory orthopnea or persistent peripheral edema despite aggressive and escalating diuretic therapy.
- Syncope or presyncope during activity, which may reflect "fixed" cardiac output secondary to RV failure.
- Non-ischemic angina chest pain, which may reflect RV myocardial ischemia due to increased RV demand.

In certain studies, physical examination often does not clearly distinguish between heart failure and pulmonary hypertension resulting from left heart disease. A systematic review and meta-analysis have assessed the diagnostic efficacy of certain bedside indicators for identifying PH, including:[13]

- Elevated jugular venous pressure (JVP): the most accurate physical sign for PH. JVP >3 cm above the sternal angle provides a combined positive likelihood ratio (LR^+) of 2.47 (95% CI 1.41–4.33).
- Right ventricular heave (RV heave): a palpable parasternal lift, indicative of pressure or volume excess in the right ventricle, has a combined LR^+ of 2.12 (95% CI 1.01–4.47)
- Loud P2: An increase in the second heart sound, which is usually most clearly heard during inspiration, is a sign of PH,[14] indicating a combined LR^+ of 1.50 (95% CI 0.96–2.33).

Although the LR value of each sign is relatively low, the presence of several signs simultaneously (e.g., increased JVP, parasternal heave, and peripheral edema) has been shown to significantly increase specificity for identifying PH. The manifestation of particular signs and symptoms of PH with heart failure is indicative of PH-LHD, necessitating further evaluation, particularly to assess the risk to the right heart.[15]

The 2023 ESC guidelines on heart failure indicate that the optimal treatment for heart failure with HFrEF comprises four foundational therapies: angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin receptor–neprilysin inhibitors (ARNI), beta blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium–glucose co-transporter 2 (SGLT2) inhibitors. Currently, the most highly recommended therapy for heart failure with preserved and middly reduced ejection fraction is SGLT2 inhibitors, but the use of ACE-I/ARB/ARNI, MRA, and beta blockers is advised solely based on the specific underlying condition. Diuretics are advised solely for heart failure accompanied by indications of fluid retention.[6]

3. Pulmonary Hypertension Left Heart Disease (PH LHD)

According to the sixth World Symposium on Pulmonary Hypertension (WSPH), Pulmonary Hypertension due to Left Heart Disease (PH-LHD) is defined as an mPAP >20 mmHg and a pulmonary artery wedge pressure (PAWP) >15 mmHg.[16] The prevalence of PH-LHD ranges from 65% to 85% of PH cases.[5] This group is further divided into two based on pulmonary vascular resistance (PVR), namely:[5]

- Isolated post-capillary PH (IpcPH): characterized by PAWP >15 mmHg and PVR <2 Wood Units (WU). This phenotype reflects passive pulmonary congestion secondary to increased left-sided filling pressures.
- Combined post- and pre-capillary PH (CpcPH): characterized by PAWP >15 mmHg and PVR >2 WU. This phenotype describes a more severe disease, in which passive congestion is accompanied by a precapillary component of active pulmonary vascular remodeling and vasoconstriction.

According to the 2022 ESC Guidelines on Pulmonary Hypertension, the causes of PH-LHD include heart failure (HFpEF, HFmrEF or HFrEF), left heart valve disease, and acquired or congenital heart disease that causes increased post-capillary pressure.

Table 2. Phenotyp and likelihood for left heart disease as cause of pulmonary hypertension.[5]

Clinical/supporting features	PH-LHD is unlikely	Intermediate probability	PH-LHD is highly likely
Age	< 60 years	60–70 years	> 70 years
Obesity, hypertension, dyslipidemia, glucose intolerance/diabetes	No risk factors	1–2 factors	> 2 factors
Known history of left heart disease (LHD)	No	Yes	Yes
History of previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Persistent/permanent
Structural LHD (e.g., LVH, significant valve disease, cardiomyopathy)	No	No	Yes
ECG	Normal or signs of RV strain	Mild LVH	LBBB or clear LVH
Echocardiography	No left atrial dilation; E/e' <13	No left atrial dilation; mitral regurgitation grade <2	Left atrial dilation (LAVI >34 mL/m^2) and/or LVH; mitral regurgitation grade ≥ 2
CPET	High VE/VCO_2 slope, without EOV	Increased VE/VCO_2 slope, with EOV	Slightly increased VE/VCO_2 slope, with EOV
cMRI	No left heart abnormalities	–	LVH; LA dilation (decreased strain or LA/RA ratio >1)

Several factors increase the likelihood of PH-LHD, including: age, risk factors for obesity, hypertension, diabetes mellitus, dyslipidemia, diagnosed left heart disease, history of cardiac intervention, atrial fibrillation, left heart structural abnormalities, electrocardiography showing LBBB or LVH, echocardiography showing left atrial dilation, LVH, and diastolic dysfunction, CPET showing increased ventilatory equivalent for carbon dioxide, and cMRI showing LVH and left atrial dilation.[5]

4. Pathophysiology PH-LHD

PH-LHD occurs in several phases that, if not optimally managed, can continuously increase the phases, ultimately resulting in right heart failure.

Phase 1 – Isolated post-capillary PH (IpcPH)

In the initial phases, left ventricular systolic or diastolic dysfunction, along with aortic and/or mitral stenosis or regurgitation, elevates left ventricular pressure, hence increasing pulmonary arterial pressure. The examination results are characterized by a PAWP >15 mmHg. This pressure is passively transmitted to the pulmonary artery, causing mPAP to increase >20 mmHg without an increase in PVR (PVR <2 WU). In this IpcPH phase, the pulmonary vasculature remains reversible, so that if congestion occurs, it can still compensate.[17]

Phase 2 – Combined post-capillary PH (CpcPH)

This phase occurs due to sustained increases in pressure that trigger changes in the pulmonary vasculature. This phase, called CpcPH, triggers vasculopathy characterized by active remodeling of the precapillary pulmonary arterioles. This process occurs due to several mechanisms, including:[18]

- Histological remodeling: prolonged pressure and shear stress, together with neurohormonal and inflammatory activation, trigger intimal hypertrophy and fibrosis as well as hypertrophy of the small pulmonary artery media.
- Pathological obstruction: these changes cause stiffness, narrowing, and pathological obstruction of the distal pulmonary vessels, resulting in a precapillary component after postcapillary congestion.

During this phase, the elevation in mPAP becomes "disproportionate" to the rise in PAWP, characterized by a PVR exceeding 2 WU, hence defining the CpcPH phenotype. At this stage, PH-LHD is no longer merely a hemodynamic problem, but an active structural pulmonary vascular disease.[11]

Phase 3 – RV–PA uncoupling and right heart failure

If CpcPH phase is not optimally managed, the increase in pulmonary vascular pressure will increase RV pressure, which, if it occurs continuously, will cause permanent right heart failure, resulting in:[19]

- Increased afterload: High PVR requires increased RV contractility to maintain cardiac output.[19]
- RV maladaptation: The RV initially hypertrophies, then dilates; this dilation causes tricuspid regurgitation (adding volume load) and septal flattening that impairs LV filling and function through the phenomenon of ventricular interdependence.[19]
- Cellular failure: At the tissue level, the right ventricle experiences maladaptive remodeling characterized by inflammation, fibrosis, and a metabolic transition from fatty acid oxidation to the less efficient glycolysis.[19]
- RV–PA uncoupling: The association between right ventricular (RV) contractility and RV afterload is referred to as RV–pulmonary artery (PA) coupling. Contractility is an inherent function of the right ventricle, and the RV and PA are considered "coupled" when RV contraction can adapt to the level of afterload. As right ventricular afterload escalates, right ventricular contractility should correspondingly enhance (by hypertrophy and adaptation to the load) to preserve right ventricular function and RV-PA coupling.

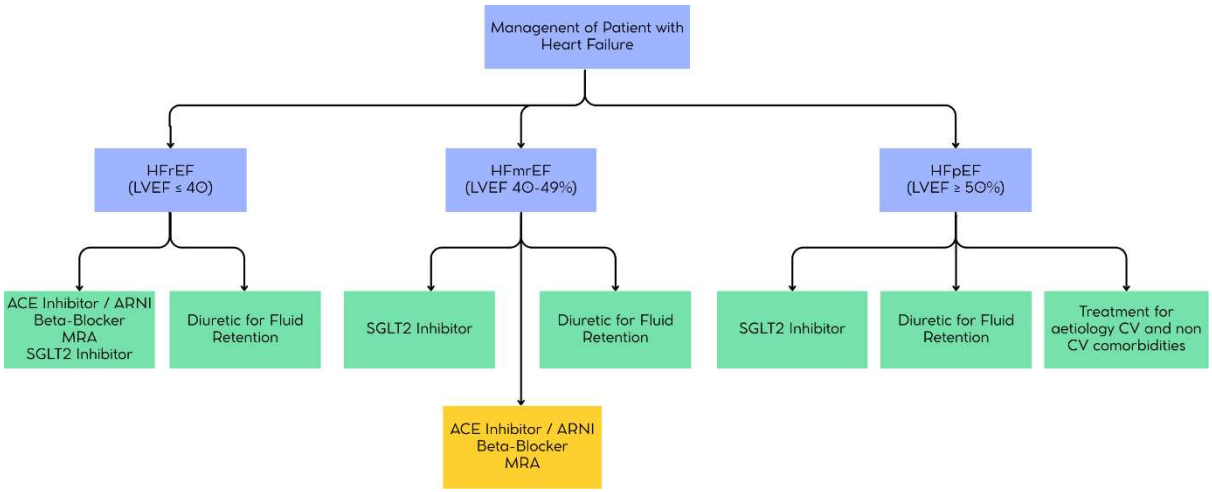

Figure 1. Management of Patient with Heart Failure.[6,9]

The primary compensatory reaction of the right ventricle to pulmonary hypertension is hypertrophy; but, if right ventricular dilatation continues, an imbalance between oxygen supply and demand may arise, leading to right ventricular ischemia and reduced contractility. At this juncture, the right ventricle is incapable of sustaining cardiac output, resulting in a "uncoupled" RV–PA connection, which clinically presents as right ventricular failure. An diminished TAPSE/sPAP ratio on echocardiography acts as a non-invasive indicator for this condition and has a substantial correlation with mortality in HF and PH-LHD.[20]

5. Non-Invasive Diagnosis PH-LHD

Echocardiography

Transthoracic echocardiography is a primary noninvasive diagnostic tool for evaluating heart failure and pulmonary hypertension following the recognition of signs and symptoms of PH-LHD.. Echocardiography can assess the likelihood of PH and determine its prognosis by evaluating its impact on the right ventricle (RV).[6]

The 2022 ESC/ERS guidelines establish a standardized algorithm for evaluating the echocardiographic likelihood of pulmonary hypertension (PH).[5]

1. Maximum tricuspid regurgitation velocity (TRVmax)

- Assessment begins with measurement of the maximum TRV. If TRV exceeds 3.4 m/s, the echocardiographic likelihood of pulmonary hypertension is classified as high.
- If TRV less than 2.8 m/s, the probability is low, provided there are no other echocardiographic signs of PH.

2. Other echocardiographic signs

- If TRVmax is in the intermediate range (2.9–3.4 m/s) or <2.8 m/s but PH is still clinically suspected, other echocardiographic signs must be assessed. The probability of pulmonary hypertension is elevated to intermediate or high if there are two or more indicators from distinct categories (A, B, or C).
- Category A (Ventricle): RV/LV basal diameter ratio >1.0; flattening of the interventricular septum (D-shape).
- Category B (Pulmonary artery): RV outflow tract (RVOT) acceleration time <105 ms and/or mid-systolic notching; pulmonary artery diameter >25 mm.
- Category C (IVC and right atrium): inferior vena cava (IVC) diameter >21 mm with inspiratory collapse <50%; right atrial area >18 cm^2.

Besides assessing the probability of pulmonary hypertension (PH), echocardiography can evaluate morbidity and mortality associated with PH.. Echocardiography can assess the RV's ability to adapt to afterload, which affects morbidity and mortality.[14]

The transition from the adaptive phase (RV hypertrophy) to the maladaptive phase (dilatation, dysfunction, and RV failure) is known as RV–RV-pulmonary artery (RV–PA) uncoupling. Although this measurement is invasive, it can be estimated accurately and simply using the TAPSE/sPAP ratio. TAPSE (Tricuspid Annular Plane Systolic Excursion) reflects RV longitudinal function as a function of RV contractility, while pulmonary artery systolic pressure (sPAP) describes afterload.[21]

A meta-analysis indicated that a reduction in the TAPSE/sPAP ratio was independently correlated with all-cause mortality, with a threshold of <0.36 mm/mmHg linked to an adjusted hazard ratio of 2.84 (95% CI 2.22–3.64). A cohort study of patients hospitalized for acute heart failure with HFpEF and HFmrEF found that a TAPSE/sPAP ratio of less than 0.38 mm/mmHg was independently linked to long-term mortality (aHR 2.21; 95% CI 1.26–3.81)[22] The conjunction of "high probability of PH" with TAPSE/sPAP <0.38 signifies a greater than twofold elevation in mortality risk and directly impacts management decisions.

Biomarkers

Cardiac biomarker testing can provide prognostic information for individuals with heart failure. NT-proBNP is the most robust and prevalent prognostic indicator in individuals with both HFrEF and HFpEF, as it reflects ventricular wall stress.[23] Other biomarker tests, such as Growth Differentiation Factor-15 (GDF-15) and soluble ST2 (sST2), can specifically provide insights into RV damage (inflammation, cell injury, and fibrosis). GDF-15 levels exceeding 1363 pg/mL and sST2 levels exceeding 38 ng/mL are correlated with right ventricular systolic dysfunction, hemodynamic anomalies, and right ventricular-pulmonary artery uncoupling, potentially indicating tissue remodeling mechanisms that differentiate passive idiopathic pulmonary hypertension from active vasculopathy in combined pre and post capillary pulmonary hypertension.[24]

6. Prognostic Determinants in PH-LHD

The most important prognostic factor in PH-LHD is increased PVR, which divides PH-LHD into CpcPH and IpcPH phenotypes. The presence of high PVR in CpcPH indicates active vascular remodeling, which continuously leads to reduced right ventricular (RV) function, heightened morbidity, and markedly increased mortality relative to passive congestion in IpcPH.

Invasive Examination (Right heart catheterization)

Right heart catheterization (RHC) is the definitive method for differentiating between CpcPH and IpcPH phenotypes.[5] This procedure should be strongly considered in high-risk groups after initial stabilization and decongestion, with the aim of establishing PVR >2 WU, confirming the CpcPH phenotype, and ruling out other etiologies.[25]

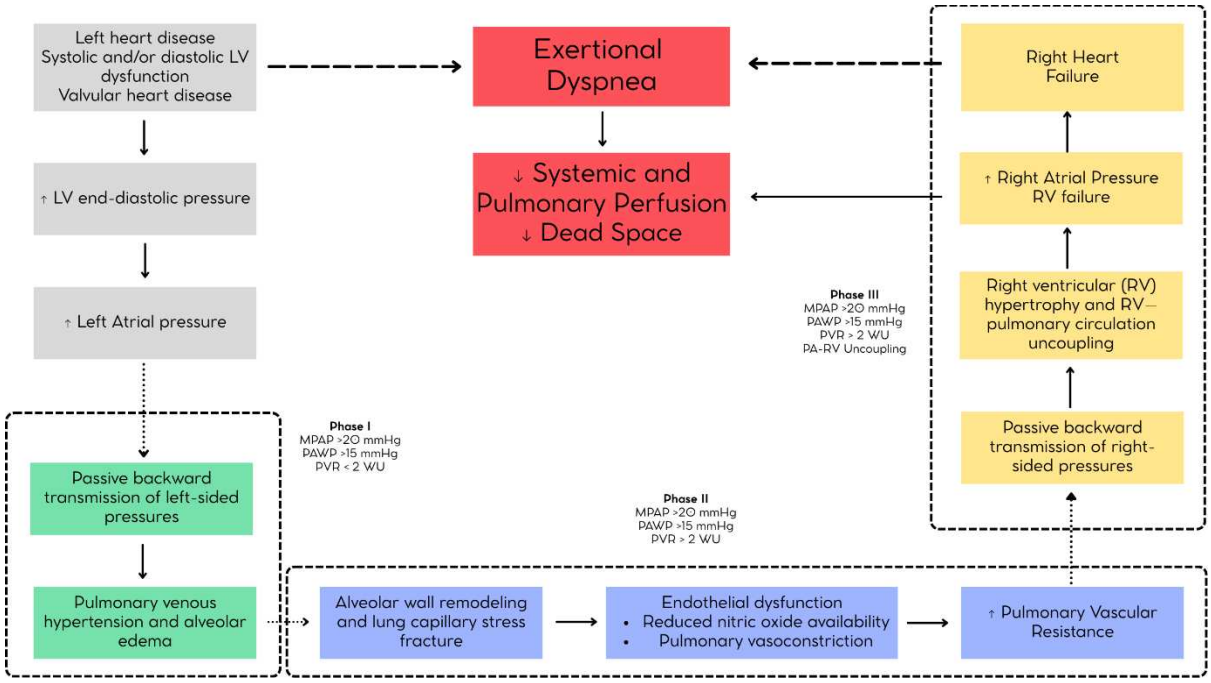

Figure 2. Pathophysiologic Mechanisms of PH-LHD.[35HFr]

A comprehensive 2022 meta-analysis by Baratto et al. involving more than 9,600 patients clarified the prognostic value of invasive markers, namely PVR and pulmonary arterial compliance (PAC) measurements obtained via RHC. PVR and PAC exhibited a stronger correlation with mortality than diastolic pressure gradient (DPG). An increase of one unit in PVR correlated with a 7% rise in event risk (HR 1.07), whereas an increase of one unit in PAC correlated with a 24% reduction in event risk (HR 0.76). The predictive significance of PVR is robust and independent of the subtype of left heart disease (e.g., HFpEF or HFrEF).[26]

These findings led to changes in the 2022 guidelines regarding the definitions of PVR (the afterload component) and PAC (reflecting pulsatile load on the RV), which are among the hemodynamic factors associated with clinical outcomes.[5] Mean right atrial pressure (mRAP) and PAWP remain strong predictors of mortality, as they reflect systemic congestion and long-term volume overload.[27]

Non-invasive Examination (Echocardiography)

Ultimately, invasive hemodynamic examination is prognostic because it describes the load on the RV. The RV's response to this load determines mortality and morbidity. Acute Hemodynamic Index (AHI), derived from Heart Rate (HR) and Pulse Pressure (PP), serves as an independent predictor of in-hospital mortality in ADHF.[28]

- RV function: Basic echocardiographic measurements of right ventricular function are robust and independent indicators of mortality. A meta-analysis of cohort studies indicates that reduced TAPSE (<17 mm), diminished RV fractional area change (RVFAC <35%), and compromised RV longitudinal strain are substantially correlated with elevated mortality in pulmonary hypertension (PH).[14]

- RV–PA coupling as a risk integrator: The right ventricular-pulmonary artery coupling ratio acts as a "prognostic tie-breaker" that can re-stratify risk within existing categories. Analysis of PAH patients showed that this ratio adds prognostic information beyond the standard ESC/ERS risk score; for example, in the "intermediate-low" risk stratum, 3-year survival was approximately 90% when the ratio was in the same stratum, but decreased to 73% when the ratio was in a different stratum.[29]

The consistency of this evidence is clear: the CpcPH phenotype with high PVR is lethal because it causes afterload, leading to RV–PA uncoupling, which is assessed non-invasively through a low TAPSE/sPAP ratio.[21] Therefore, the primary goal of non-invasive screening is to identify uncoupling.

7. PH-LHD Therapy

Therapeutic implications for PH-LHD can be derived from the risk stratification framework, which is based on the following three main principles.

- **Optimization of Basic GDMT Therapy**
  Management of patients with group 2 PH involves aggressive management of underlying left heart disease in accordance with guidelines. Management involves diuretics to diminish PAWP and the optimization of the four pillars of GDMT for heart failure: RAAS blockade/ARNI, beta-blockers, MRA, and SGLT2 inhibitors.[30]

- **Initiation of in-hospital therapy in "High Risk" patients**
  In patients who have a high probability of PH and indications of RV–PA uncoupling, GDMT-directed therapy should be initiated immediately and optimized during hospitalization.

  - SGLT2 inhibitor: In the EMPULSE randomized trial involving 530 patients stabilized after ADHF across all LVEF categories, the administration of empagliflozin 10 mg during hospitalization yielded a clinically significant benefit at 90 days (win ratio 1.36) and decreased the occurrence of serious adverse events compared to placebo (32.3% vs. 43.6%). A comprehensive review of patient data from several groups of pulmonary hypertension patients indicated that the administration of SGLT2 inhibitors was correlated with a decrease in all-cause mortality, right ventricular failure, and hospitalization, with a hazard ratio of approximately 0.71.[31]

  - ARNI in HFrEF: In the PIONEER-HF trial involving 881 patients with ADHF and HFrEF, the initiation of ARNI during hospitalization led to a more significant reduction in NT-proBNP levels compared to enalapril, without an increase in the incidence of renal impairment, hyperkalemia, or symptomatic hypotension. The advantages of ARNI persisted uniformly across high-risk patient populations.[32]

- **Avoid specific PAH vasodilators (contraindicated)**
  All major international guidelines (ESC/ERS, AHA) explicitly do not recommend the off-label use of specific PAH drugs (e.g., PDE5 inhibitors such as sildenafil, endothelin receptor antagonists such as bosentan, or sGC stimulators such as riociguat) in the PH-LHD population.[30] This is due to, among other things:

  - Lack of efficacy: Several clinical trials in PH-LHD with these drugs showed neutral results or failed to improve clinical outcomes.[33]

  - Risk of harm: The use of these medications elevates the risk of fluid retention, exacerbates heart failure, and poses the significant threat of severe pulmonary edema. Pulmonary edema occurs due to several mechanisms, including: 1. In PH-LHD, the main "obstruction" is high postcapillary pressure (PAWP >15 mmHg) due to a stiff/unable-to-accommodate-volume LV. 2. Precapillary vasodilators such as sildenafil dilate the pulmonary arterioles, causing a sharp increase in blood flow to the already congested capillaries. 3. The non-compliant LV is unable to accommodate this volume surge, leading to rapid increases in capillary pressure and fluid transudation into the alveoli, triggering acute pulmonary edema.[16]

  Thus, identifying a high probability of PH in HF patients is not an indication for PAH medication but a strong contraindication; therapeutic focus should remain on optimizing GDMT-s and correcting left heart disease, especially in patients with the high-risk CpcPH phenotype.[16]

8. Conclusion

PH-LHD is a complication of left heart failure that lacks adequate treatment. Early detection of pulmonary hypertension from symptoms and signs and non-invasive examinations in hospitalized heart failure patients can accelerate the diagnosis of PH and improve prognosis without waiting for invasive examinations, which are considered the gold standard for PH diagnosis. The prognosis of PH-LHD is influenced not only by pressure but also by degree *of RV–PA uncoupling*. RV–PA uncoupling can be accurately and noninvasively estimated using echocardiography by measuring the ratio TAPSE/sPAP; a value <0.38 mm/mmHg identifies high-risk patients with a more than twofold increase in mortality. In patients with a "High Risk" profile (a high probability of pulmonary hypertension and right ventricular-pulmonary artery uncoupling), there is an increased morbidity and mortality, warranting the initiation of in-hospital heart failure medication in alignment with guideline-directed medical therapy, utilizing SGLT2 inhibitors and ARNI. In these patients, the use of particular PAH vasodilators, within the setting of PH-LHD, may provide considerable hazards, including abrupt pulmonary edema. Investigation is required regarding the morbidity and mortality of heart failure patients with an high probability of pulmonary hypertension who undergo early initiation therapy with ARNI/SGLT2 inhibitors.

9 . Declaration

9.1 Ethics Approval and Consent to participate
Not applicable.

9.2. Consent for publication
Not applicable.

9.3 Availability of data and materials
Data used in our study were presented in the main text.

9.4 Competing interests
Not applicable.

9.5 Funding Source
Not applicable.

9.6 Authors contributions
Idea/concept: MAR. Design: MAR. Control/supervision: VY. Data collection/processing: MAR. Extraction/Analysis/interpretation: MAR, VY. Literature review: MAR, VY. Writing the article: MAR. Critical review: VY. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

9.7 Acknowledgements
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