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Diagnostic and Prognostic Use of Biomarkers in Group 2 Pulmonary Hypertension: A Comprehensive Review

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Abstract

Background: Pulmonary hypertension due to left heart disease (PH-LHD; Group 2) is the most prevalent form of PH, yet its diagnosis and differentiation from precapillary forms remain challenging. This review evaluates the role of established and emerging biomarkers in improving diagnosis, risk stratification, and monitoring.

Methods: A comprehensive literature review was conducted focusing on the pathophysiology and clinical utility of circulating biomarkers in PH-LHD phenotypes, including isolated postcapillary (IpcPH) and combined pre- and postcapillary (CpcPH) disease.

Results: Natriuretic peptides (BNP/NT-proBNP) and high-sensitivity troponins are robust predictors of mortality and right ventricular (RV) failure but are limited by low specificity and confounding factors like obesity and renal function. Inflammatory and fibrotic markers, such as galectin-3 and sST2, provide insights into maladaptive remodeling. Endothelial biomarkers (vWF, GDF-15) and metabolic signatures assist in identifying the transition to CpcPH, which carries a significantly worse prognosis. Emerging molecular tools, including microRNAs (e.g., miR-21) and extracellular vesicles, offer potential for high-precision phenotyping but require large-scale validation.

Conclusion: Integrating biomarkers into clinical practice enhances the sensitivity of echocardiographic screening and invasive hemodynamics. A multi-marker strategy is essential to capture the heterogeneity of PH-LHD, accounting for systemic comorbidities such as obesity and metabolic syndrome. Future research should prioritize standardizing "omics" platforms to facilitate personalized therapeutic interventions.

Keywords: Pulmonary hypertension due to left heart disease (PH-LHD); Biomarkers; Right ventricular failure; Natriuretic peptides; Hemodynamic

Abbreviations: AF: Atrial Fibrillation; ANP: Atrial Natriuretic Peptide; BNP: B-type Natriuretic Peptide; BCAAs: Branched-Chain Amino Acids; BMI: Body Mass Index; CA-125: Cancer Antigen 125; CKD: Chronic Kidney Disease; CpcPH: Combined Pre- and Postcapillary Pulmonary Hypertension; CRP: C-Reactive Protein; cTn: Cardiac Troponin (cTnI, cTnT); CT-proET-1: C-terminal pro-Endothelin-1; DPG: Diastolic Pressure Gradient; ECM: Extracellular Matrix; ET-1: Endothelin-1; GDF-15: Growth Differentiation Factor-15; HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; hs-cTn: High-sensitivity Cardiac Troponin; IVC: Inferior Vena Cava; IpcPH: Isolated Postcapillary Pulmonary Hypertension; LHD: Left Heart Disease; miRNA: MicroRNA; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; PA: Pulmonary Artery; PAH: Pulmonary Arterial Hypertension; PAP: Pulmonary Arterial Pressure; PAWP: Pulmonary Artery Wedge Pressure; PH: Pulmonary Hypertension; PVR: Pulmonary Vascular Resistance; RV: Right Ventricle / Right Ventricular; sST2: Soluble ST2; TAPSE: Tricuspid Annular Plane Systolic Excursion; TRV: Tricuspid Regurgitation Velocity; vWF: von Willebrand Factor; WHO: World Health Organization

Introduction

Pulmonary hypertension due to left heart disease (PH-LHD), classified as World Health Organization (WHO) Group 2 pulmonary hypertension, represents the most common form of pulmonary hypertension worldwide [1,2]. PH-LHD is hemodynamically defined by a mean pulmonary artery pressure greater than 20mmHg with an elevated pulmonary arterial wedge pressure greater than 15mmHg on right heart catheterization [2,3]. This condition develops through the passive backward transmission of elevated left-sided filling pressures in the setting of heart failure, either with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF), as well as in the context of valvular heart disease and other left-sided cardiac pathologies [1,4]. PH-LHD can be further subdivided into isolated postcapillary pulmonary hypertension, characterized by pulmonary vascular resistance less than 3 Wood units, and combined pre- and postcapillary pulmonary hypertension, with pulmonary vascular resistance of 3 Wood units or greater, reflecting different degrees of pulmonary vascular remodeling and carrying distinct prognostic implications [2,3].

Despite its high prevalence, the accurate diagnosis and classification of PH-LHD presents substantial clinical challenges. Differentiating PH-LHD from other pulmonary hypertension groups, particularly WHO Group 1 pulmonary arterial hypertension (PAH), remains a critical yet often difficult task with important therapeutic implications [5,6]. Clinical features such as advanced age, presence of metabolic syndrome comorbidities including systemic hypertension and coronary artery disease, and echocardiographic evidence of left ventricular dysfunction suggest PH-LHD rather than PAH [2,5]. However, many patients present with overlapping clinical phenotypes, normal left ventricular ejection fraction, and no severe valvular lesions, making the distinction particularly challenging [5].

Furthermore, some patients with PH-LHD may develop superimposed pulmonary vascular disease with a precapillary component, adding additional diagnostic complexity [5]. The heterogeneity of PH-LHD, variations in hemodynamic assessment techniques, and the influence of fluid status and heart failure treatment on hemodynamic parameters further complicate accurate phenotyping and risk stratification [2,7]. In this complex diagnostic landscape, biomarkers have emerged as valuable tools with multiple potential clinical applications in PH-LHD. For screening purposes, biomarkers may help identify patients at risk for developing pulmonary hypertension among those with established left heart disease, potentially enabling earlier intervention [8].

In the diagnostic realm, biomarkers can assist in differentiating PH-LHD from other forms of pulmonary hypertension and in characterizing specific hemodynamic phenotypes, particularly when invasive testing is not immediately available or feasible [8,9]. Prognostically, biomarkers provide crucial information for risk stratification, helping clinicians identify patients at higher risk for adverse outcomes including right ventricular failure, hospitalization, and mortality [8,10]. Additionally, biomarkers may serve an important role in therapy monitoring, assessing response to treatment and guiding adjustments in management strategies, though this application remains an area of active investigation [8].

The aim of this comprehensive review is to systematically summarize the current state of knowledge regarding established biomarkers in PH-LHD, critically evaluate emerging biomarkers that show promise for clinical application, and explore future directions in biomarker research that may ultimately improve the diagnosis, risk stratification, and management of this prevalent and challenging condition.

Epidemiology and Clinical Context

In patients with heart failure (HF) and valvular disease, circulating biomarkers reflect underlying myocardial stress, inflammation, fibrosis, and neurohormonal activation. Across the spectrum of HF, natriuretic peptides such as B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are consistently elevated, particularly in decompensated states, and correlate with severity of symptoms and hemodynamic burden. In addition to natriuretic peptides, markers of myocardial injury (troponins), extracellular matrix turnover (galectin-3, ST2), and renal dysfunction are frequently abnormal, highlighting multi-organ involvement in advanced disease states. In valvular heart disease, elevated natriuretic peptides similarly signal increased wall stress due to volume or pressure overload; increased levels of troponin and inflammatory markers have also been documented, reflecting ongoing myocardial strain and remodeling in the context of chronic valvular lesions [11].

Within the heart failure population, HF with preserved ejection fraction (HFpEF) complicated by pulmonary hypertension (PH) demonstrates a distinct biomarker profile characterized by disproportionately high natriuretic peptide levels relative to left ventricular systolic function, reflecting increased left atrial pressure and pulmonary vascular load. Biomarkers associated with fibrosis and inflammation, including galectin-3 and soluble ST2, are often elevated in HFpEF with PH and correlate with worse exercise tolerance and adverse outcomes, underscoring the role of systemic and pulmonary vascular remodeling in this phenotype (2). Conversely, HF with reduced ejection fraction (HFrEF) with PHtypically shows markedly elevated natriuretic peptides in conjunction with higher troponin levels, driven by ongoing myocyte injury and pronounced neurohormonal activation. In HFrEF, elevations in markers of renin-angiotensin-aldosterone system activity and catecholamine turnover further distinguish this phenotype, reflecting more severe ventricular dysfunction and greater susceptibility to hemodynamic decompensation [12].

In valvular disease–associated pulmonary hypertension, the biomarker profile is heavily influenced by the type and

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chronicity of the lesion. Patients with longstanding mitral or aortic valve disease leading to PH often exhibit elevated BNP/NT-proBNP that correlates with severity of pulmonary pressures and functional class, accompanied by increased troponin indicative of ventricular strain. Markers of extracellular matrix remodeling and inflammation have also been reported, supporting the contribution of both left-sided pressure overload and pulmonary vascular changes to the observed hemodynamic derangements [11].

The comparison between combined post-capillary and pre-capillary PH (CpcPH) and isolated post-capillary PH (IpcPH) reveals further biomarker distinctions. In IpcPH, elevations in natriuretic peptides predominate, consistent with passive backward transmission of elevated left atrial pressure without significant pulmonary vascular remodeling. In contrast, CpcPH shows not only elevated natriuretic peptides but also higher levels of biomarkers associated with vascular remodeling (e.g., endothelin-1, inflammatory cytokines) and right ventricular dysfunction, reflecting a superimposed pre-capillary pulmonary vascular pathology. These differences underscore the more aggressive disease and worse prognosis seen in CpcPH compared with IpcPH [13]. Collectively, these biomarker patterns enhance phenotypic characterization, provide insights into underlying pathophysiology, and may inform risk stratification and therapeutic approaches across HF and valvular disease spectrums.

Pathophysiology Basis for Biomarker Use

The release of both ANP and BNP is increased in heart failure (HF), as ventricular myocytes are stimulated to secrete both ANP and BNP in response to increased strain caused by high ventricular filling pressures and increased exposure to neurohormones (eg, norepinephrine and angiotensin). The plasma concentrations of both hormones are increased in patients with asymptomatic and symptomatic left ventricular (LV) dysfunction, permitting their use in diagnosis. Both B-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) have diuretic, natriuretic, and vasodilator effects. They also inhibit the renin-angiotensin system, endothelin secretion, and systemic and renal sympathetic activity. Among patients with HF, increased secretion of BNP and ANP may partially counteract the effects of norepinephrine, endothelin, and angiotensin II, limiting the degree of vasoconstriction and sodium retention [14].

Cell death is preceded by a substantial reversible pre-lethal phase. However, ongoing myocardial stress, depending on the mechanism and extent of myocardial stress, may lead to different forms of cell death. When myocardial necrosis occurs, lysosomal enzymes degrade the contractile filaments, and the integrity of the plasmalemma is disrupted. Cardiomyocytes rapidly release intracellular macromolecules into the interstitial space. cTn shows a rapid increase after myocardial injury, comparably fast to cytosolic proteins. There, additional proteolysis of troponins may occur, e.g., by matrix metalloproteinase-2 or thrombin. Notably, however, the currently commercially available routine hs-cTnT assay, which utilizes antibodies targeting the amino acid fragment 125–147, is unaffected by thrombin-mediated cTnT degradation. Local blood and lymphatic flow also influence the onset of the subsequent cTn increase in the systemic circulation. For example, early reperfusion of the infarct-related coronary artery results in more rapid extraction and clearance of cTn from damaged myocardium [15].

The increase of pressure triggers remodelling and stiffening of both pulmonary arteries (PA) and pulmonary veins, contributing to an additional rise in pulmonary vascular resistance (PVR), which marks the transition from isolated post-capillary pulmonary hypertension (IpcPH) to combined post- and pre-capillary pulmonary hypertension (CpcPH). In LHD patients, PH significantly increases morbidity and mortality by increasing the hemodynamic load on the right ventricle (RV), first by leading to adaptive hypertrophy followed by dilatation and ultimately failure. Smooth muscle cell (SMC) hyperplasia represents a hallmark of pulmonary vascular remodelling in pulmonary arterial hypertension (PAH). Hyperproliferation and hypertrophy of resident SMCs have been proposed to drive SMC hyperplasia, resulting in occlusive pulmonary vascular remodelling. From small PAs and arterioles, SMCs migrate further into the distal lung vasculature, leading to vessel muscularization, stiffening, and occlusion. A growing body of evidence implicates extracellular matrix (ECM) remodelling, including basement membrane (BM) remodelling, as a significant factor in the pathogenesis of PH. PA ECM remodelling in both PAH and PH-LHD is characterized by an increased expression and crosslinking of fibrillar collagens and as such promotes vascular stiffening [16].

Beyond vasoconstrictive and proliferative responses mediated by ET-1, increased secretion of inflammatory cytokines and growth factors (e.g., transforming growth factor alpha 1, TGF-α1; vascular endothelial growth factor, VEGF; and interleukin 1, IL1) have also been associated with structural and functional changes in response to the retrograde increase in pulmonary capillary pressure. Among them, the role of vascular endothelial growth factor-D (VEGF-D) has been recently evaluated in PH-LHD. VEGF-D is a secreted factor that regulates angiogenesis, lymphangiogenesis and vascular permeability. It is synthesized and secreted as a large precursor, which is subsequently proteolytically processed at both N- and C-termini to yield the mature forms. Unprocessed VEGF-D is selective for vascular endothelial growth factor receptor 3 (VEGFR-3), which is mainly expressed in lymphatic endothelial cells, whereas the mature VEGF-D activates both VEGFR-3 and VEGFR-2, the latter of which is found in both vascular and lymphatic endothelial cells. Besides modulating the growth of blood and lymphatic vessels, VEGF-D has been shown to induce cardiac fibrogenesis by stimulating myofibroblast growth, migration, and type I collagen synthesis.

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VEGF-D has also been shown to be up-regulated by mechanistic (formerly mammalian) target of rapamycin (mTOR), a master regulator of cell growth, proliferation, and survival that has been implicated in PAH, lymphangioleiomyomatosis (LAM), and cancer [8].

Precapillary pulmonary hypertension (pPH) causes increased right ventricular (RV) afterload, inducing RV remodeling. The prognosis of patients with PH is not solely determined by pulmonary arterial pressure or pulmonary vascular resistance. Various studies have shown that the ability of the RV to adequately adapt to increased pressure loading is essential for a patient's prognosis. If RV adaptation is not adequate, pPH will often result in RV dysfunction and dilatation, heart failure, and ultimately death. Right atrial (RA) dilatation and functional decline, caused by increased RV end-diastolic pressure and tricuspid regurgitation, is also associated with prognosis. The RV attempts to adapt to the increased pulmonary vascular resistance in pPH by increasing its contractility. RV remodeling, such as hypertrophy and changes in muscle properties, ensures that stroke volume can be maintained in the early stages. When these mechanisms fall short in later stages, the RV dilates and the heart rate increases, and RVEF decreases.. Since a decline in RVEF will only occur in later stages of heart failure, earlier markers of changed RV function would be valuable for guidance of medical therapy and follow-up of pPH patients [17].

Established Biomarkers

Natriuretic Peptides (BNP, NT-proBNP)

B-type natriuretic peptide (BNP) is a neurohormone synthesized by myocytes in response to increased parietal stress from pressure or volume overload. Its precursor, proBNP, is cleaved into the biologically active BNP and the inactive NT-proBNP [18,19]. In Group 2 pulmonary hypertension (PH-LHD), plasma levels rise proportionally to pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), reflecting both left and right heart congestion [18,20,21]. However, "low-proBNP" phenotypes exist, particularly in obese patients with heart failure and preserved ejection fraction (HFpEF), where markers may be disproportionately low despite high filling pressures [18].

Current evidence does not support specific BNP/NT-proBNP thresholds to reliably distinguish between isolated post-capillary (IpcPH) and combined pre- and post-capillary pulmonary hypertension (CpcPH) [18,22,23]. While elevations correlate with right ventricular (RV) dysfunction and atrial dilatation, they reflect hemodynamic repercussions rather than specific etiologies [23-25]. Standard cutoffs (e.g., BNP >100 pg/mL) lack the sensitivity and specificity needed for phenotypic discrimination, which still requires invasive hemodynamics [18,23]. Despite this, the prognostic value of these peptides regarding mortality and hospitalization remains well-established [19,26,27]. In acute heart failure, BNP levels ≥840 pg/mL are associated with a significant increase in in-hospital mortality (6% vs. 1.9%) [19,26]. NT-proBNP >986 pg/mL at admission is a powerful predictor of 1-year mortality [10], and a reduction of >30% during hospitalization signals a lower risk of readmission, whereas an increase identifies high-risk patients [19]. Meta-analyses indicate that every 100 pg/mL increment in BNP correlates with a 14% increase in mortality risk [28].

Clinical interpretation must account for renal function, obesity, and atrial fibrillation (AF) [18,19]. Chronic kidney disease (CKD) impairs clearance, leading to elevated levels—especially for NT-proBNP-even in the absence of heart failure [18]. Obesity is associated with lower BNP levels due to increased peripheral clearance, which can mask the severity of PH-LHD [18,20]. Conversely, AF increases levels due to atrial remodeling, potentially decreasing diagnostic specificity [29].

7.2. Cardiac Troponins (cTnI, cTnT, hs-cTn)

Cardiac troponins are essential markers of subclinical myocardial injury in PH-LHD [19,30]. Persistent wall stress and hemodynamic overload induce myocyte apoptosis and protein degradation, leading to troponin release without acute ischemic necrosis [19,31]. Even modest elevations detected by high-sensitivity assays correlate with progressive functional decline and adverse remodeling [19,30]. Troponin elevation in patients with RV dysfunction is a robust predictor of mortality and hospitalization, independent of other biomarkers [19,32]. In hospitalized patients, positive troponin status is linked to higher in-hospital mortality (8% vs. 2.7%) and longer hospital stays [19,32]. This pattern holds across various heart failure etiologies and reflects myocardial damage secondary to chronic pressure overload on the right ventricle [32,33].

In the context of HFpEF and HFrEF phenotypes associated with PH, chronic troponin elevation is common [18,30]. While data on which phenotype presents higher concentrations are conflicting, absolute differences are generally modest [30]. In HFpEF, hs-cTnT levels correlate with increased filling pressures and severity of PH during exercise, reflecting a lack of myocardial reserve [18]. In both groups, elevated high-sensitivity troponins identify high-risk subgroups with similar prognostic implications [18,30,34].

Inflammatory and Fibrotic Biomarkers in PH-LHD

The onset, course, and prognosis of pulmonary hypertension brought on by left heart disease are significantly influenced by inflammation and fibrosis. C-reactive protein (CRP), galectin-3, and soluble ST2 (sST2) are examples of developing biomarkers that offer complementary insights into unfavorable clinical outcomes, cardiac and vascular remodeling, and systemic inflammation.

C-Reactive Protein (CRP)

The acute-phase reactant C-reactive protein is produced in response to inflammatory signaling mediated by interleukin-6. Elevated CRP in PH-LHD is a sign of persistent systemic

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inflammation caused by congestion, tissue hypoperfusion, left heart failure, and neurohormonal activation [35,36]. According to Quarck et al. (2009), there is a correlation between high-sensitivity CRP levels and pulmonary hemodynamic severity, such as pulmonary artery pressure and pulmonary vascular resistance, suggesting that inflammatory load follows the course of the disease [37]. Even after controlling for traditional risk factors, persistently increased CRP is an independent predictor of heart failure hospitalization and cardiovascular death. According to Paulus and Tschöpe (2013), persistent inflammation facilitates the transition from isolated post-capillary pulmonary hypertension to combined pre- and post-capillary illness by causing endothelial dysfunction, pulmonary vascular remodeling, and cardiac fibrosis [36].

Galectin-3

In cardiovascular disease, galectin-3, a lectin produced by macrophages, actively drives fibrotic remodeling. Myocardial stiffness and a prolonged increase in left-sided filling pressures are caused by elevated galectin-3, which also stimulates fibroblast activation, collagen deposition, and extracellular matrix expansion [38]. Galectin-3 is linked to left ventricular and pulmonary vascular remodeling in PH-LHD, especially during the shift to fixed pulmonary vascular disease. Independent of natriuretic peptides, elevated galectin-3 levels are clinically strongly linked to heart failure hospitalization, mortality, and disease progression, highlighting its function as a marker of maladaptive structural remodeling rather than hemodynamic stress alone [38].

Soluble ST2 (sST2)

Myocardial strain and pressure overload cause the production of soluble ST2, which acts as a decoy receptor to block the cardioprotective interleukin-33/ST2L signaling pathway. Elevated pulmonary and systemic pressures in PH-LHD cause the left and right ventricular myocardium to emit sST2, which reflects biomechanical stress and active remodeling [39]. Increased sST2 causes progressive myocardial fibrosis, hypertrophy, and ventricular dysfunction via opposing IL-33-mediated anti-fibrotic signaling. Strong predictive information is provided by elevated sST2 levels, which, when assessed serially, give dynamic risk stratification and independently predict mortality and heart failure hospitalization beyond natriuretic peptides [39].

Clinical Implications

CRP, galectin-3, and sST2 are three distinct yet interconnected fibrotic and inflammatory processes that are crucial to the pathogenesis of PH-LHD. To improve outcomes in PH-LHD, their combined evaluation improves risk stratification, detects patients with progressive pulmonary vascular remodeling, and supports new approaches that target inflammation and fibrosis [36].

Endothelial Dysfunction and Vascular Remodeling Biomarkers

Endothelin-1

Represents a key biomarker reflecting pulmonary vasoconstriction and vascular remodeling in PH-LHD. This potent vasoconstrictor peptide is produced by endothelial cells in response to various stimuli including hypoxia, inflammation, and mechanical stress [8,40]. In the pathophysiology of PH-LHD, increased endothelin expression contributes to a superimposed precapillary component that combines pulmonary vasoconstriction, decreased nitric oxide availability, and progressive vascular remodeling [40]. Plasma levels of C-terminal pro-endothelin-1 (CT-proET-1), a stable surrogate marker for endothelin-1, are elevated in patients with heart failure with preserved ejection fraction (HFpEF) and correlate strongly with mean pulmonary artery pressure, pulmonary capillary wedge pressure, and inversely with pulmonary artery compliance [41]. Higher CT-proET-1 levels are associated with worse right ventricular diastolic reserve, reduced cardiac output responses to exercise, and more severely impaired peak oxygen consumption in HFpEF patients with pulmonary hypertension [41].

Despite its pathophysiologic relevance, the clinical utility of endothelin-1 as a diagnostic biomarker in PH-LHD is limited by substantial overlap with WHO Group 1 pulmonary arterial hypertension, where endothelial dysfunction and increased endothelin activity are also prominent features [40,42]. This lack of specificity restricts its ability to differentiate between PH-LHD and other forms of pulmonary hypertension, though it may provide valuable information regarding disease severity and the presence of pulmonary vascular remodeling within the PH-LHD population [7,8].

von Willebrand factor (vWF)

vWF serves as an important marker of endothelial injury and dysfunction in pulmonary hypertension. This large multimeric glycoprotein is synthesized by endothelial cells and released in response to endothelial activation and damage [43]. Elevated plasma vWF levels have been consistently demonstrated in patients with pulmonary arterial hypertension and are associated with hemodynamic severity [43,44]. In pulmonary hypertension, vWF antigen levels correlate with pulmonary vascular resistance and other measures of hemodynamic impairment, reflecting the degree of endothelial injury in the pulmonary vasculature [43,44].

Importantly, vWF has demonstrated prognostic value across various forms of pulmonary hypertension. Higher baseline vWF levels independently predict increased risk of death or lung transplantation in patients with pulmonary arterial hypertension, with this association persisting even after adjustment for

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demographics, hemodynamics, and other laboratory parameters. Similarly, elevated vWF levels at follow-up remain associated with worse survival, suggesting that persistent endothelial injury despite treatment may impact disease course [43].

The prognostic significance of vWF appears to extend beyond its hemostatic effects, as the ratio of ristocetin cofactor activity to vWF antigen (which reflects platelet binding capacity) does not predict outcomes, indicating that vWF's prognostic value relates more to its role as a marker of endothelial dysfunction rather than its coagulation properties [43,45]. While most studies of vWF in pulmonary hypertension have focused on WHO Group 1 disease, the biomarker's reflection of endothelial injury makes it potentially relevant for assessing vascular dysfunction in PH-LHD, though specific data in this population remain limited [42].

Growth Differentiation Factor-15 (GDF-15)

GDF-15 has emerged as a promising biomarker in pulmonary hypertension, reflecting multiple pathophysiologic processes including oxidative stress, inflammation, and cellular injury. GDF-15 is a stress-responsive cytokine belonging to the transforming growth factor-β superfamily that is expressed in response to various cellular stresses including ischemia, oxidative stress, inflammation, and mitochondrial dysfunction [46,47]. In cardiovascular disease, GDF-15 is produced by cardiac myocytes, macrophages, vascular smooth muscle cells, endothelial cells, and adipocytes under conditions of metabolic or oxidative stress [46,48]. In patients with idiopathic pulmonary arterial hypertension, elevated GDF-15 levels are associated with increased mean right atrial pressure, pulmonary capillary wedge pressure, lower mixed venous oxygen saturation, and higher levels of uric acid and N-terminal pro-BNP [49].

GDF-15 demonstrates strong prognostic value for predicting mortality and right ventricular dysfunction in pulmonary hypertension. In adults with pulmonary hypertension (excluding Group 2), elevated GDF-15 levels are independently associated with increased risk of death or lung transplantation, with this association remaining significant even after adjustment for age and NT-proBNP [50]. Patients with normal GDF-15 levels show 100% event-free survival at 2 years compared to 72.4% in those with elevated levels [50]. Recent evidence suggests that incorporating GDF-15 into existing risk stratification models, such as COMPERA, improves their discriminatory ability for mortality prediction in pulmonary arterial hypertension [51]. Changes in GDF-15 levels over time correlate with changes in NT-proBNP and mixed venous oxygen saturation, suggesting that GDF-15 may be useful for monitoring disease progression and treatment response [49]. While GDF-15 is a non-specific biomarker elevated in various cardiovascular and systemic conditions, its ability to capture chronic disease burden, oxidative stress, and inflammation makes it particularly valuable for identifying low-risk patients and enhancing prognostic assessment in pulmonary hypertension [47,50].

Renal, Hepatic, and Metabolic Biomarkers

Role of Renal Dysfunction Biomarkers in Risk Prediction

In pulmonary hypertension caused by left heart disease (PH-LHD), renal impairment is a crucial comorbidity that has a substantial impact on prognosis and treatment results. When compared to traditional creatinine-based evaluations, cystatin C, a 13-kDa cysteine protease inhibitor, has become a better biomarker for the early identification of renal impairment in cardiovascular disease states [52]. In patients with cardiac cachexia, which is frequently seen in severe heart failure, its production is independent of muscle mass, age, and sex, offering more precise glomerular filtration assessment.

Elevated cystatin C levels are an independent predictor of poor outcomes in PH-LHD, such as mortality, hospitalization for heart failure, and development of combined pre- and post-capillary pulmonary hypertension (CpcPH) [53]. Elevated pulmonary venous pressure causes systemic venous congestion, decreased renal perfusion, and neurohormonal activation that further impairs renal function. This pathological cycle is created by the cardiorenal interaction. Research shows that hemodynamic severity and right ventricular dysfunction are associated with even slight increases of cystatin C (>1.0mg/L). Comprehensive multi-organ evaluation and more accurate prognostication in PH-LHD are made possible by the incorporation of cystatin C into risk stratification algorithms, especially when paired with natriuretic peptides and hepatic congestion markers [52,53].

Congestion Biomarkers: CA-125 and Hepatic Injury Enzymes

One of the main characteristics of advanced PH-LHD is systemic venous congestion, with certain biomarkers showing significant clinical utility. Through mechanical stress on mesothelial cells lining the pericardium, pleura, and peritoneum, cancer antigen 125 (CA-125), initially a diagnostic for ovarian cancer, reflects serosal inflammation and fluid accumulation in heart failure [54]. CA-125 levels in patients with PH-LHD are highly correlated with hemodynamic congestion indices such as hepatic venous pressure, pulmonary capillary wedge pressure, and right atrial pressure. Increased mortality, hospitalization for heart failure, and decreased functional ability are all linked to elevated CA-125 (>35U/mL). Significantly, repeated assessments offer a dynamic assessment of decongestion throughout therapy; declining levels signify a positive response to treatment. Beyond myocardial stretch, the predictive effect of CA-125 captures distinct pathophysiological elements of congestion and appears to be independent of and additive to natriuretic peptides [54].

Liver enzyme patterns are indicative of hepatic congestion caused by increased right-sided filling pressures. Centrilobular hepatocyte necrosis and fibrosis from chronic venous hypertension are reflected in the "congestive hepatopathy" pattern of chronic

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passive hepatic congestion in PH-LHD, which is characterized by mild transaminase elevations with AST/ALT ratios greater than 1, frequently accompanied by elevated alkaline phosphatase and gamma-glutamyl transferase [55]. Hepatorenal syndrome, death, and progressive right heart failure are all predicted by elevated transaminases, especially if they persist despite treatment. More severe chronic congestion with the potential to develop into cardiac cirrhosis is indicated by AST/ALT ratios greater than 1.5. Integration of hepatic biomarkers with CA-125 and natriuretic peptides enables comprehensive congestion burden assessment, facilitating risk stratification and therapeutic decision-making [55].

Metabolic Signature Alterations in PH-LHD

Hemodynamic stress, neurohormonal activation, and reduced cellular energy generation are the causes of metabolic abnormalities in PH-LHD. Metabolomic profiling can identify significant abnormalities in substrate usage, mitochondrial function, and intermediate metabolism caused by advanced heart failure and pulmonary hypertension [56]. Impaired glucose management, increased lipolysis with raised free fatty acids, ketone body buildup, and disruptions in amino acid metabolism are some of these alterations. Energy deprivation and increasing cardiac failure result from the failing heart's metabolic inflexibility, which shifts toward glucose oxidation despite insulin resistance [56].

A number of metabolites have been identified as biomarkers of clinical significance. Branched-chain amino acids (BCAAs) are associated with worse outcomes and more severe disease because they build up as a result of hepatic metabolic impairment and muscle breakdown. The gut microbiota produces trimethylamine N-oxide (TMAO), which is linked to higher mortality and thrombotic risk in heart failure. Cardiac and pulmonary vascular remodeling are influenced by altered ceramides and sphingolipids [56]. Different metabolic phenotypes are identified by metabolomic profiling; significant abnormalities, such as increased BCAAs, decreased citric acid cycle intermediates, and acylcarnitine buildup, are associated with increased risks of hospitalization and mortality. These metabolic markers may also differentiate between combined pre- and post-capillary PH (CpcPH) and isolated post-capillary PH (IpcPH), with CpcPH exhibiting more severe dysfunction as a result of further pulmonary vascular disease. Precision phenotyping and targeted metabolic treatments may be made possible by combining metabolomic data with conventional biomarkers [56].

Emerging Molecular Biomarkers

Emerging molecular biomarkers represent an expanding field of interest in the evaluation of Group 2 pulmonary hypertension (PH-LHD), particularly in light of the persistent limitations of conventional circulating biomarkers for accurate phenotyping and non-invasive risk stratification. Advances in molecular profiling have highlighted the potential role of microRNAs, metabolomic and proteomic signatures, and extracellular vesicles as integrative indicators of pulmonary vascular stress, endothelial dysfunction, and maladaptive cardiopulmonary interactions, although their clinical applicability remains largely investigational [57-65].

MicroRNAs (miRNAs)

Circulating microRNAs (miRNAs) have been increasingly recognized as central regulators of gene expression pathways involved in pulmonary vascular remodeling, inflammation, and endothelial dysfunction. Specific miRNAs such as miR-21, miR-26a, and miR-328 have been implicated in key mechanisms underlying pulmonary hypertension, including smooth muscle cell proliferation, extracellular matrix remodeling, and altered calcium signaling [57-59]. miR-21, in particular, has been associated with fibrotic and proliferative responses within the pulmonary vasculature, processes that may be accentuated in PH-LHD in the context of chronic venous congestion and elevated left-sided filling pressures [57,58]. Importantly, differential miRNA expression profiles have been described between PH-LHD and pulmonary arterial hypertension (PAH), suggesting a potential role for miRNA-based signatures in distinguishing post-capillary and combined pre- and post-capillary phenotypes from primary pulmonary vascular disease [60].

Metabolomics and Proteomics

Beyond transcriptomic regulation, metabolomic and proteomic approaches have provided novel insights into the molecular heterogeneity of PH-LHD. High-throughput metabolomic analyses have identified distinct alterations in amino acid metabolism, lipid signaling pathways, and mitochondrial energy utilization in patients with combined pre- and post-capillary pulmonary hypertension (CpcPH), differentiating this subgroup from isolated post-capillary disease [61,62]. These metabolic derangements are thought to reflect impaired myocardial–pulmonary vascular coupling, oxidative stress, and endothelial nitric oxide dysregulation. Complementary proteomic studies have further identified differential expression of inflammatory mediators, extracellular matrix proteins, and endothelial signaling molecules associated with disease severity and adverse outcomes. Despite their mechanistic relevance, these platforms remain in early translational phases, with limited standardization and a lack of large-scale validation cohorts restricting their current clinical utility [63].

Extracellular Vesicles and Exosomes

Extracellular vesicles, including exosomes, have recently emerged as promising biomarkers due to their ability to convey biologically active cargo reflective of cellular stress, endothelial injury, and inflammatory activation. Increased circulating levels of endothelial-derived extracellular vesicles have been observed in pulmonary hypertension and are associated with

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vascular dysfunction and unfavorable hemodynamic profiles [64]. Given their relative stability in circulation and accessibility through minimally invasive sampling, extracellular vesicles may offer future opportunities for dynamic disease monitoring and therapeutic response assessment in PH-LHD. However, significant methodological challenges, including heterogeneity in isolation techniques and analytic platforms, must be addressed before their integration into routine clinical practice [65].

Integrating Biomarkers into Clinical Practice

Diagnosis

Diagnosis begins with NT-proBNP screening and standardized echocardiography [66]. While NT-proBNP is widely used, its limited specificity necessitates integration with imaging. Echocardiographic suspicion of PH is based on peak tricuspid regurgitation velocity (TRV), RV dilation, septal flattening, and IVC distension according to ESC guidelines [66-71]. Precise assessment includes TAPSE for longitudinal RV function and Simpson's formula for LV ejection fraction to identify underlying left-heart etiologies.

Identifying Probable CpcPH

CpcPH is hemodynamically defined by a pulmonary artery wedge pressure (PAWP) >15mmHg and a diastolic pressure gradient (DPG) ≥7mmHg (or PVR >2 WU) [67,68]. Molecularly, CpcPH resembles PAH more than IpcPH, suggesting severe intrinsic vascular remodeling beyond passive congestion [71,72]. Emerging data suggest genetic predispositions and metabolic syndrome may drive this progression toward a precapillary phenotype in LHD patients.

Risk Stratification

Integrating established markers—BNP, troponins, and ST2—improves the prediction of RV failure and mortality. Detectable serum cardiac troponin T serves as a critical marker of poor prognosis in patients with chronic pulmonary hypertension [70]. Baseline NT-proBNP levels correlate strongly with RV hemodynamics and serve as a critical independent predictor of long-term survival.

Treatment Monitoring

Management focuses on optimizing left-sided filling pressures. Group 2 PH is a common complication of valvular disease or left-heart failure, significantly increasing morbidity [68,72]. Monitoring hemodynamic changes helps assess the transition from passive IpcPH to the higher-risk CpcPH.

Limitations

Comorbidities significantly confound biomarker interpretation. Strict blood pressure control according to newly established guidelines is essential to reduce cardiovascular mortality [73]. Obesity (BMI ≥35kg/m^2) and specific fat distribution patterns are directly linked to the development of incident hypertension and metabolic complications that exacerbate PH-LHD [74].

Conclusion

Pulmonary hypertension due to left heart disease (PH-LHD) remains a complex clinical entity where precise phenotyping—specifically distinguishing between IpcPH and CpcPH—is paramount for management. While NT-proBNP and cardiac troponins are established as cornerstones for screening and risk stratification, their lack of specificity for pulmonary vascular remodeling necessitates a multi-marker approach. Integrating inflammatory markers (CRP, sST2), endothelial signals (vWF, GDF-15), and extracardiac indicators (Cystatin C, CA-125) offers a more holistic view of the heart-lung-kidney axis. Emerging omics-based biomarkers and microRNAs hold promise for non-invasive "liquid biopsies," but standardization is required before clinical adoption. Ultimately, biomarkers should complement, not replace, clinical judgment and invasive hemodynamics to optimize therapeutic strategies in this high-risk population.

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