

Role of Novel Biomarkers in Early Detection of Rare Pulmonary Cardiovascular Disorders

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Abstract: Cardiovascular diseases, including rare pulmonary cardiovascular disorders, represent a critical area where early detection significantly impacts clinical outcomes. Novel biomarkers have emerged as vital tools for improving diagnostic accuracy, risk stratification, and prognosis beyond traditional clinical assessments. These biomarkers reflect various pathophysiological processes such as myocardial injury, inflammation, vascular dysfunction, and fibrosis, which are central to pulmonary cardiovascular disease progression. Examples include natriuretic peptides, cardiac troponins, galectin-3, ST2, mid-regional pro-adrenomedullin, and microRNAs, which offer insight into disease mechanisms and early molecular changes. A multi-marker approach combining these novel biomarkers enhances the capability to identify disease at a subclinical stage, enabling timely intervention and improved patient management. Ongoing research and technological advances in genomics, proteomics, and metabolomics are poised to further expand biomarker discovery, fostering better risk prediction and personalized therapeutic strategies for these complex disorders. Importantly, biomarkers should be integrated with clinical and imaging data for comprehensive evaluation and decision-making.

Keywords: Novel biomarkers, Mid-regional pro-adrenomedullin, microRNAs, multi-marker approach, Diagnostic challenges, Risk prediction, Prognosis, Biomarker clinical implementation, Personalized medicine, cardiovascular disease biomarkers, Screening in at-risk populations.

INTRODUCTION

Rare pulmonary cardiovascular disorders encompass a group of uncommon diseases primarily affecting the blood vessels and heart structures involved in pulmonary circulation. These include conditions such as pulmonary arterial hypertension (PAH), pulmonary heart disease, hereditary hypertrophic cardiomyopathy, transthyretin amyloid cardiomyopathy, and certain congenital heart defects affecting pulmonary vasculature. These diseases are characterized by abnormalities in pulmonary artery pressure, vascular remodelling, and right heart dysfunction, affecting fewer than 1 in 2,000 individuals, which often leads to challenges in diagnosis and management due to their rarity and clinical complexity[1][2].

Early detection of these rare disorders is critical for preventing progressive vascular and cardiac damage that can culminate in right heart failure and mortality. Because of their subtle and overlapping symptoms with more common respiratory diseases, delayed diagnosis frequently occurs, worsening prognosis. Timely identification through sensitive tools leads to earlier therapeutic interventions that can modify disease trajectory, improve quality of life, and reduce mortality [3][4].

Overview of novel biomarkers and their potential role in early detection:

Novel biomarkers have emerged as powerful tools for early detection and risk assessment in rare pulmonary cardiovascular disorders[5]. These biomarkers reflect underlying pathophysiological mechanisms such as myocardial stress, inflammation, fibrosis, and endothelial dysfunction. Compared to traditional clinical assessments, novel biomarkers enable more precise and earlier recognition of disease before overt clinical manifestations, thus allowing for tailored management strategies and improved outcomes. Combining multiple biomarkers enhances diagnostic accuracy and prognostic evaluation in these complex diseases. [6].

CURRENT CHALLENGES IN EARLY DETECTION

Lack of specific symptoms for rare pulmonary cardiovascular disorders:

Symptoms of rare pulmonary cardiovascular disorders, such as pulmonary arterial hypertension (PAH), are often non-specific and overlap with more common respiratory diseases like asthma, COPD, and left heart disease. Common symptoms include shortness of breath, fatigue, and weakness, which are easily mistaken for other conditions. This lack of specific early symptoms leads to low clinical suspicion and hinders timely diagnosis [7][8].

Delay in diagnosis due to reliance on traditional diagnostic methods:

The diagnosis of these disorders typically depends on traditional methods such as echocardiography, chest X-rays, pulmonary function tests, and right heart catheterization. These approaches, while valuable, often detect disease at advanced stages because early signs may be subtle or missed. Data show mean delays of 2–3 years from symptom onset to diagnosis in PAH despite advances in diagnostic techniques. Misdiagnosis or exclusion of other more common diseases further delays proper identification and treatment [9][10].

Rare pulmonary cardiovascular disorders suffer from limited awareness among healthcare providers and the public, which contributes to under-recognition and under-diagnosis. Screening is often not prioritized due to resource constraints and the rarity of these diseases. Additionally, comorbidities in aging populations complicate screening efforts. Consequently, at-risk populations do not receive timely or adequate screening, impacting early detection and intervention. These challenges underscore the need for enhanced diagnostic tools such as novel biomarkers that can complement traditional methods and improve early recognition of rare pulmonary cardiovascular diseases.

Role of Novel Biomarkers in Early Detection

Biomarkers are measurable indicators of normal biological processes, pathogenic processes, or responses to therapeutic interventions. They may be molecular, biochemical, cellular, or physiological characteristics that can be objectively measured and evaluated to identify the presence or severity of a disease. In medical diagnosis, biomarkers serve as critical tools for early detection, predicting disease risk, monitoring progression, and evaluating treatment efficacy. They can be found in various biological samples like blood, urine, or tissues and range from proteins and genes to metabolites and physiological parameters [11].

In rare pulmonary cardiovascular disorders, several novel biomarkers reflect the underlying disease mechanisms such as myocardial stress, inflammation, fibrosis, and endothelial dysfunction. These include natriuretic peptides (e.g., BNP, NT-pro BNP) that indicate cardiac strain, cardiac troponins as markers of myocardial injury, galectin-3 and ST2 relating to fibrosis and remodelling, mid-regional pro-adrenomedullin indicating vascular stress, and microRNAs reflecting early molecular changes. These biomarkers provide nuanced, earlier insights into disease presence and progression than traditional diagnostic modalities. [12][13]

Advantages of using novel biomarkers in early detection compared to traditional methods:

Novel biomarkers offer higher sensitivity and specificity for detecting rare pulmonary cardiovascular disorders in their subclinical stages, when symptoms are absent or

non-specific. Unlike traditional methods that often identify disease at advanced stages, biomarkers can detect molecular and cellular changes early in the disease course. Additionally, a multi-marker approach combining several biomarkers enhances diagnostic accuracy and allows personalized risk stratification, facilitating earlier and targeted therapeutic interventions. Biomarkers also enable non-invasive or minimally invasive monitoring of disease progression and treatment response. In summary, novel biomarkers play a pivotal role in early detection by providing objective, sensitive, and specific measures of disease biology that complement and extend beyond conventional diagnostic techniques, improving patient outcomes in rare pulmonary cardiovascular disorders [14][15].

CASE STUDIES AND RESEARCH FINDINGS

Numerous studies have demonstrated the value of novel biomarkers in the early detection and prognosis of pulmonary arterial hypertension (PAH), a paradigm rare pulmonary cardiovascular disorder. For example, circulating angiogenic modulatory factors such as soluble endoglin and sVEGFR1 have been found elevated in PAH patients and correlate with disease severity. Heart function biomarkers like B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-pro BNP) have shown strong predictive value for disease progression and mortality. Emerging cardiovascular biomarkers including mid-regional pro-adrenomedullin (MR-pro ADM), high-sensitivity troponin T, and lipid-related markers like HDL cholesterol also provide complementary information on disease status and prognosis. These studies highlight how a multi-marker approach encompassing different biological pathways can improve early diagnosis and monitoring

Patients diagnosed and monitored using panels of novel biomarkers tend to have better risk stratification and tailored treatment plans compared to those relying solely on traditional clinical and imaging methods. For instance, NT-pro BNP levels not only predict survival but also treatment efficacy, allowing therapeutic adjustments aimed at achieving biomarker targets. Novel biomarkers can detect subtle physiological changes before echocardiographic or hemodynamic evidence appears, enabling earlier intervention. While large-scale comparative outcome trials remain limited, existing evidence suggests biomarker-guided care improves prognosis and reduces healthcare costs by preventing advanced disease complications

Future research is focused on validating promising biomarkers through large multi center cohorts and developing sensitive, specific assays suitable for routine clinical use. There is growing interest in discovering biomarkers representing diverse pathological compartments, including pulmonary vasculature,

inflammation, extracellular matrix remodelling, and right ventricular function. Challenges include standardization of assay techniques, integrating biomarker panels with clinical workflows, regulatory approvals, and cost-effectiveness considerations. Additionally, no single biomarker may suffice, underscoring the need for multi-marker strategies tailored to individual patient phenotypes to optimize

early detection and personalized management. In summary, clinical research supports the utility of novel biomarkers in enhancing early detection, risk stratification, and prognosis in rare pulmonary cardiovascular disorders, while ongoing studies aim to overcome hurdles for their widespread clinical adoption and maximize patient benefit

RESULT:

BNP and NT-pro BNP (red): B-type natriuretic peptides, important for detecting cardiac stress and heart failure, commonly elevated in pulmonary hypertension and right ventricular dysfunction. ST2 (dark blue): A marker of cardiac fibrosis and remodelling—high levels indicate myocardial stress and adverse cardiac remodelling. Galectin-3 (purple): Linked to inflammation and fibrosis, significant in tissue remodelling and progression of cardiovascular disease. Tn (high sensitivity troponin, brownish-grey): Indicates myocardial injury and damage even at very low levels, useful for detecting subtle myocardial stress in pulmonary vascular diseases. IMA (Ischemia-modified albumin, dark green): Reflects ischemic injury to cardiac tissue. CECs (Circulating endothelial cells, grey): Elevated in vascular injury or damage, indicative of endothelial dysfunction which is essential in pulmonary hypertension. miRNAs (microRNAs, salmon pink): Small non-coding RNAs that regulate gene expression; specific miRNAs are emerging as sensitive biomarkers for early molecular changes in cardiovascular and pulmonary vascular disease. Lp-PLA2 (lipoprotein-associated phospholipase A2, bright green): An enzyme linked to vascular inflammation and atherosclerosis, reflective of vascular pathology. CRP (C-reactive protein, bright blue): A general inflammation marker that is elevated in systemic inflammatory states, including vascular inflammation. FABP (Fatty acid-binding protein, black): Reflects myocardial injury and can provide early detection of cardiac damage. MR-pro ADM (mid-regional pro-adrenomedullin, pink): Indicates vascular stress and endothelial dysfunction, connected to disease severity in pulmonary vascular disorders. GDF-15 (growth differentiation factor-15, brown): Associated with oxidative stress and inflammation, serving as a prognostic biomarker.

Table 1:

Disease	Key Novel Biomarkers	Utility
Pulmonary Arterial Hypertension (PAH)	BMPR2 mutations, NT-proBNP, miR-210, GDF-15	Risk assessment, diagnosis, prognosis
Pulmonary Veno-Occlusive Disease (PVOD)	EIF2AK4 mutations, vascular endothelial growth factor (VEGF)	Genetic diagnosis, differentiation from PAH
CTEPH	D-dimer, fibrin degradation products, miRNAs	Screening post-PE, noninvasive follow-up
Heritable PAH	Genetic panel (BMPR2, ALK1, ENG)	Family screening, early intervention
Sarcoidosis-associated PH	ACE levels, IL-2 receptor, chitotriosidase	Supporting diagnosis, inflammation tracking

Novel biomarkers play a critical role in the early detection of rare pulmonary cardiovascular disorders such as pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease (PVOD), and chronic thromboembolic pulmonary hypertension (CTEPH) in table 1. These conditions are often difficult to diagnose in their early stages due to non-specific symptoms and low prevalence. Biomarkers—including genetic mutations (like BMPR2 and EIF2AK4), circulating proteins (such as NT-proBNP, GDF-15, and VEGF), microRNAs, and metabolic profiles—provide valuable molecular insights that can indicate disease before structural changes appear on imaging. For instance, NT-proBNP is already used to detect right heart strain in PAH, while genetic testing can identify individuals at risk for heritable forms of the disease. Emerging biomarkers like microRNAs and extracellular vesicles offer potential for non-invasive screening and differentiation between similar disorders.

CONCLUSION

Rare pulmonary cardiovascular disorders are challenging to detect early due to non-specific symptoms, diagnostic delays, and limited awareness. Novel biomarkers offer a promising solution by providing sensitive, specific, and objective measures of underlying pathophysiology including myocardial stress, inflammation, fibrosis, and vascular dysfunction. Studies highlight biomarkers such

as natriuretic peptides, cardiac troponins, galectin-3, ST2, mid-regional pro-adrenomedullin, and microRNAs as effective tools for earlier diagnosis, risk stratification, and prognosis compared to traditional methods. The multi-marker approach combining several biomarkers better captures disease complexity and enhances clinical decision-making. Incorporating novel biomarkers into early detection strategies can bridge critical gaps in

identifying rare pulmonary cardiovascular disorders at subclinical stages. This can lead to timelier interventions, tailored treatments, and improved patient outcomes including reduced morbidity and mortality. Novel biomarkers complement existing imaging and hemodynamic assessments to provide a more comprehensive, real-time evaluation of disease status and therapeutic response. Ongoing research to validate novel biomarkers in large diverse cohorts and developing cost-effective, standardized assays is essential. Integrating biomarker panels into routine clinical workflows requires collaboration among researchers, clinicians, regulatory agencies, and industry. Emphasis should be placed on overcoming implementation challenges, educating providers, and expanding screening in high-risk populations. With these efforts, novel biomarkers have the potential to transform the diagnostic landscape and optimize care for patients with rare pulmonary cardiovascular disorders.

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