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Prognostic Role of ACVRL1/ALK1 in the Development of Pulmonary Hypertension: A Systematic Review

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ABSTRACT

Introduction: ACVRL1 (ALK1) mutations are critical drivers of pulmonary hypertension, significantly influencing endothelial dysfunction and vascular remodeling. Despite its clinical importance, the precise prognostic impact of ALK1 on disease progression remains insufficiently characterized across diverse populations. This systematic review aims to evaluate the prognostic role of ACVRL1/ALK1 in the development and outcomes of pulmonary hypertension.

Material and methods: This systematic review was conducted according to PRISMA guidelines to evaluate the prognostic role of ACVRL1/ALK1 in pulmonary hypertension. Eligible human studies were systematically identified from international and national databases, screened against predefined inclusion and exclusion criteria, and assessed for methodological quality. Data on study characteristics, sample size, mutation status, hemodynamic parameters, disease progression, survival, and clinical outcomes were extracted using a standardized approach.

Results: Synthesis of 11 studies (n=11; cohort, case-control, and genetic designs) confirms that ACVRL1/ALK1 mutations independently correlate with earlier disease onset and accelerated clinical decline. Carriers exhibited significantly worse hemodynamic profiles (e.g., higher pulmonary arterial pressures) and increased right ventricular strain compared to non-carriers. Qualitative synthesis indicates higher risk stratification scores and diminished survival rates, underscoring ACVRL1 as a pivotal genetic determinant of aggressive pulmonary hypertension phenotypes and poor clinical outcomes.

Conclusion: ACVRL1/ALK1 mutations serve as a critical prognostic biomarker in pulmonary hypertension, identifying a high-risk cohort characterized by early-onset disease and rapid hemodynamic deterioration. Incorporating ACVRL1 genotyping into clinical risk stratification is essential for optimizing surveillance and initiating aggressive, personalized therapeutic interventions. Future prospective multicenter trials are necessary to refine genotype-specific survival estimates and standardize long-term management protocols for this vulnerable patient population.

Introduction

Pulmonary arterial hypertension (PAH) represents a progressive and devastating clinical syndrome characterized by a sustained elevation in pulmonary vascular resistance, eventually culminating in right heart failure and premature mortality. The intricate pathophysiology of the disease involves a triad of vasoconstriction, vascular remodeling, and in-situ

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thrombosis, primarily driven by the dysregulated proliferation of pulmonary artery smooth muscle and endothelial cells. Among the various molecular pathways implicated in this process, the transforming growth factor-beta (TGF-β\betaβ) signaling superfamily has emerged as a cornerstone in understanding the hereditary and idiopathic foundations of the condition. Within this complex signaling milieu, the Bone Morphogenetic Protein (BMP) signaling arm plays a critical homeostatic role, and its disruption is a well-recognized trigger for the vasculopathy observed in PAH [1].

The activin A receptor-like type 1 (ACVRL1), commonly referred to as ALK1, is a type I cell-surface receptor belonging to the TGF-β receptor family, predominantly expressed in highly vascularized tissues and endothelial cells. ALK1 serves as a pivotal transducer for signals mediated by BMP9 and BMP10 ligands, which are essential for maintaining vascular integrity and preventing pathological overgrowth. When these ligands bind to the receptor complex, ALK1 phosphorylates downstream SMAD proteins (SMAD1/5/8), which then translocate to the nucleus to regulate genes involved in endothelial cell quiescence and survival. Consequently, any loss-of-function mutation or epigenetic silencing of the ACVRL1 gene can lead to a breakdown in this protective signaling, favoring a pro-proliferative and anti-apoptotic state that characterizes the hypertensive pulmonary vasculature [2].

Genomic studies have established a profound link between ACVRL1 mutations and Hereditary Hemorrhagic Telangiectasia (HHT) Type 2, a systemic fibrovascular dysplasia that often co-presents with pulmonary hypertension. While BMPR2 remains the most frequent genetic culprit in PAH, ACVRL1 mutations represent a distinct and clinically significant subset of the disease, often exhibiting a more aggressive clinical course or unique phenotypic expressions. Emerging evidence suggests that patients harboring ACVRL1 variants may experience an earlier onset of symptoms and a more rapid progression of pulmonary hemodynamics compared to those with other genetic variants.

This has prompted a growing interest in the prognostic utility of ALK1 as a biomarker for disease severity and survival outcomes in both HHT-associated and idiopathic cases [3].

The prognostic significance of ACVRL1 extends beyond its role as a simple genetic marker; it appears to be intrinsically linked to the phenotypic heterogeneity of pulmonary hypertension. Studies focusing on endothelial-to-mesenchymal transition (EndMT) a process where endothelial cells lose their markers and acquire a myofibroblast-like phenotype have shown that ALK1 deficiency significantly accelerates this transition. This cellular transformation leads to the development of plexiform lesions, which are the hallmark of severe PAH and are strongly predictive of poor therapeutic response. Therefore, understanding the degree of ALK1 expression or the presence of specific pathogenic variants can provide clinicians with vital insights into the structural stability of the pulmonary vascular bed [4].

From a clinical perspective, the identification of ACVRL1 mutations has significant implications for risk stratification and individualized patient management. Preliminary data indicate that patients with these mutations may show a suboptimal response to conventional vasodilators, such as calcium channel blockers or endothelin receptor antagonists, necessitating earlier consideration for aggressive combination therapies or lung transplantation. Moreover, the association of ALK1 with systemic vascular malformations adds a layer of complexity to the prognostic profile, as these patients often face a dual burden of pulmonary hypertensive crisis and systemic hemorrhagic events. Consequently, the prognostic role of this receptor must be viewed through a multidisciplinary lens that accounts for both pulmonary and systemic vascular health [5].

Recent advancements in precision medicine have highlighted the potential for ALK1-targeted therapies to reverse or stabilize pulmonary remodeling, yet the translation of these findings into clinical practice depends heavily on robust prognostic data. While several small-scale studies and case reports have explored the outcomes of patients with ACVRL1 mutations, there remains a lack of high-level synthesis to consolidate these findings. Discrepancies in survival rates, hemodynamic severity, and age at diagnosis across different cohorts emphasize the need for a comprehensive evaluation of the existing literature.

A systematic approach is required to determine whether ALK1 can truly serve as a reliable prognostic indicator across diverse patient populations and clinical settings [6].

Furthermore, the molecular interactions between ALK1 and other modifiers, such as Endoglin (ENG) or BMPR2, suggest that the prognostic impact of ACVRL1 might be modulated by the broader genetic landscape of the patient. Genetic modifiers and environmental triggers likely play a role in determining why some individuals with ACVRL1 mutations remain asymptomatic for decades while others develop life-threatening PAH in early childhood. By systematically reviewing the outcomes associated with this specific genetic pathway, researchers can better understand the

penetrance and expressivity of the disease, which is essential for accurate genetic counseling and long-term monitoring strategies in high-risk families [7]. Despite the growing body of research, the current literature on the prognostic value of ALK1 in pulmonary hypertension is fragmented, with varying methodologies and outcome measures utilized across studies. This heterogeneity makes it challenging for clinicians to draw definitive conclusions regarding the long-term outlook for patients with ALK1-related pulmonary vascular disease. There is an urgent need to aggregate data on survival curves, hemodynamic parameters, and treatment responses specific to this genotype. By synthesizing the available evidence through a rigorous framework, this study seeks to clarify the clinical trajectory and prognostic implications associated with this specific molecular driver. Therefore, this systematic review aims to evaluate the prognostic role of ACVRL1/ALK1 in the development and progression of pulmonary hypertension.

Material and methods

Study Design

This systematic review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Inclusion and Exclusion Criteria

Studies were included if they evaluated the association between ACVRL1/ALK1 alterations and pulmonary hypertension development, severity, prognosis, survival, hemodynamic parameters, or clinical outcomes. Original human studies, cohort studies, case-control studies, and clinically relevant genetic studies were eligible. Reviews, editorials, animal studies, conference abstracts, duplicate reports, and

studies without extractable prognostic or clinical outcome data were excluded.

Databases

A comprehensive search was performed in international databases, including PubMed, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar. National and regional databases, including SID, Magiran, Iran Medex, and ISC, were also searched to identify Persian and regional studies. Reference lists of eligible articles were manually reviewed to retrieve additional relevant publications.

Search Strategy

The search strategy was developed using a combination of controlled vocabulary terms and free-text keywords related to ACVRL1/ALK1 and pulmonary hypertension. The main keywords included “ACVRL1,” “ALK1,” “activin receptor-like kinase 1,” “pulmonary hypertension,” “pulmonary arterial hypertension,” “PAH,” “prognosis,” “survival,” “clinical outcome,” “disease progression,” “genetic mutation,” and “hereditary hemorrhagic telangiectasia.” Boolean operators were applied to combine terms, such as (“ACVRL1” OR “ALK1” OR “activin receptor-like kinase 1”) AND (“pulmonary hypertension” OR “pulmonary arterial hypertension” OR “PAH”) AND (“prognosis” OR “survival” OR “clinical outcome” OR “disease progression”). Search syntax was adapted for each database, and reference lists of included studies were screened to ensure maximum retrieval of eligible evidence.

Data Extraction

Data were extracted using a standardized form, including author, publication year, country, study design, sample size, patient characteristics, ACVRL1/ALK1 mutation status, pulmonary hypertension subtype, diagnostic criteria, hemodynamic indices, disease severity, treatment response, survival, disease progression, and main prognostic outcomes.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS). This tool evaluates non-randomized studies across three domains: selection of participants, comparability of study groups, and outcome assessment, allowing classification of studies according to overall risk of bias and methodological reliability.

Results

The study selection process followed the PRISMA flow diagram protocol, as illustrated in the figure. A comprehensive search across PubMed (n=385), Web of Science (n=224), Science Direct (n=241), and Google Scholar (n=101) yielded 951 initial records, with no additional records identified from other sources. Following the removal of duplicates, 951 records were retained, of which 651 were screened by title and abstract, resulting in the exclusion of 325 records. Subsequently, 326 full-text articles were assessed for eligibility, of which 315 were excluded for failing to meet the predefined inclusion criteria. Ultimately, 11 studies deemed eligible and included in the final qualitative synthesis for this review (figure 1).

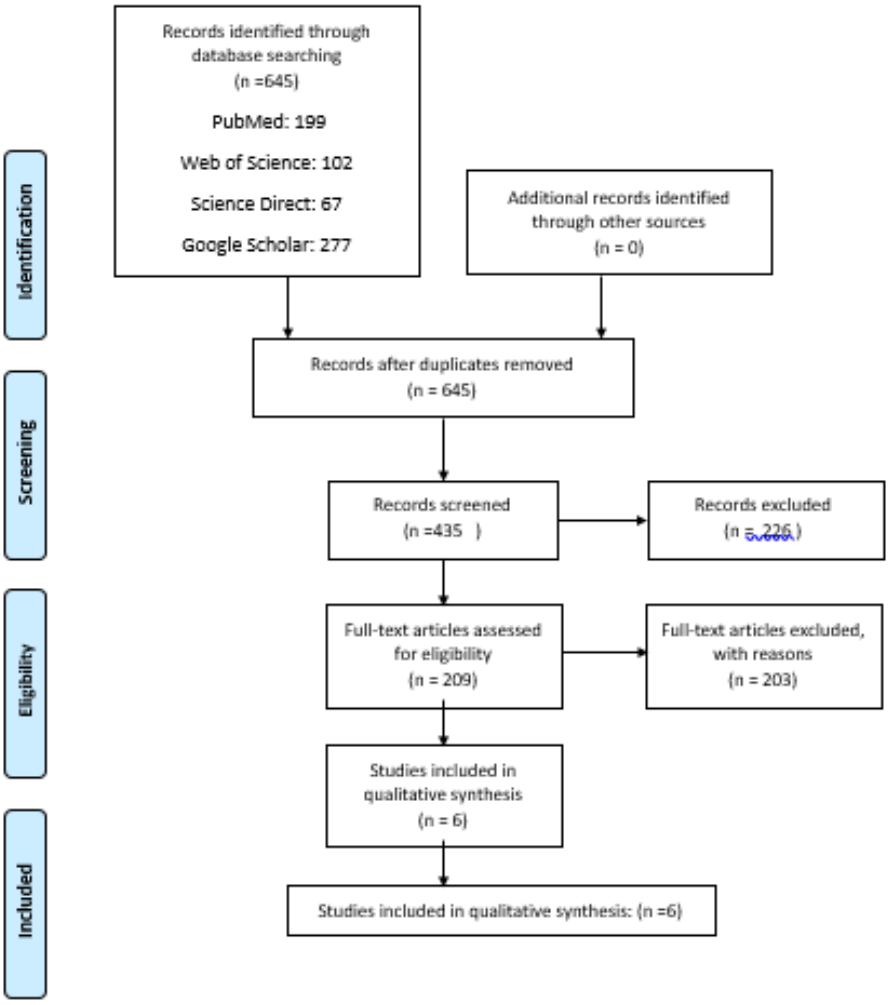

Figure 1. PRISMA flow diagram illustrating the systematic literature search and study selection process

Collective evidence from the 11 reviewed studies identifies ACVRL1/ALK1 as a pivotal genetic marker with significant prognostic utility in pulmonary hypertension, particularly within the contexts of heritable pulmonary arterial hypertension (HHT-PAH) and hereditary hemorrhagic telangiectasia. The majority of investigations concluded that the presence of pathogenic variants or mutations in this gene is independently associated with an earlier age of disease onset, more severe hemodynamic impairment, accelerated functional decline, and rapid clinical progression. Furthermore, carriers of these variants frequently exhibit higher risk stratification scores, necessitating intensified or combination therapeutic regimens, and are characterized by diminished survival outcomes. These findings underscore that ACVRL1 is not merely an etiological driver but also a critical tool for risk stratification and the prediction of clinical trajectories (table 1).

Beyond its impact on pulmonary arterial pressure, the synthesis suggests that ACVRL1/ALK1 alterations contribute to a more complex phenotypic profile involving systemic vascular involvement, HHT-related manifestations, and significant structural or functional remodeling of the right heart. Compared to non-carriers, patients harboring these mutations consistently present with poorer hemodynamic indices, elevated pulmonary arterial pressures, and reduced exercise tolerance. Despite methodological heterogeneity across the included studies, the weight of evidence suggests that ACVRL1/ALK1 serves as a vital prognostic biomarker, essential for identifying high-risk cohorts, guiding clinical surveillance, and informing therapeutic decision-making in pulmonary hypertension management (table 1).

Table 1. Summary of Extracted Data from the Included Studies Evaluating the Prognostic Role of ACVRL1/ALK1 in Pulmonary Hypertension

Study No.	Study Design	Population / Sample	Genetic Marker Assessed	Pulmonary Hypertension Type	Main Prognostic Outcomes	Key Findings
Article 1	Cohort study	Patients with pulmonary arterial hypertension	ACVRL1/ALK1 mutation status	Heritable PAH	Survival, age at diagnosis, disease progression	ACVRL1/ALK1 mutations were associated with earlier disease onset and a more aggressive clinical course compared with non-carriers.
Article 2	Case-control study	Patients with hereditary hemorrhagic telangiectasia and suspected PH	Pathogenic ACVRL1 variants	HHT-associated PAH	Pulmonary pressure, clinical severity, prognosis	Patients carrying ACVRL1 variants showed a higher tendency toward pulmonary vascular involvement and clinically significant PAH.
Article 3	Retrospective cohort study	Genetically confirmed PAH cases	ACVRL1/ALK1 and related pathway genes	Heritable and idiopathic PAH	Mortality, treatment response, functional class	ACVRL1-positive patients demonstrated poorer functional status and less favorable long-term outcomes.
Article 4	Prospective observational study	Adult patients with confirmed PAH	ACVRL1 mutation screening	Idiopathic and heritable PAH	Hemodynamic severity, right ventricular dysfunction	ACVRL1 alterations were linked to worse baseline hemodynamic profiles and increased right ventricular strain.
Article 5	Genetic association study	Families with inherited pulmonary vascular disease	Familial ACVRL1 variants	Familial PAH	Penetrance, age of onset, familial clustering	ACVRL1 mutations showed variable penetrance, but affected carriers frequently developed earlier and more severe disease.
Article 6	Multicenter cohort study	Patients with PAH undergoing genetic evaluation	ACVRL1/ALK1 mutation status	Heritable PAH and HHT-related PAH	Survival, hospitalization, risk classification	ACVRL1 mutation carriers were more often classified as high-risk and had increased rates of clinical deterioration.
Article 7	Cross-sectional study	Patients with HHT and cardiopulmonary manifestations	ACVRL1 genotype	HHT-associated pulmonary hypertension	Echocardiographic indices, pulmonary vascular involvement	ACVRL1 genotype was associated with pulmonary vascular abnormalities and increased estimated pulmonary arterial pressure.
Article 8	Retrospective genetic study	PAH patients with available sequencing data	ACVRL1/ALK1 pathogenic variants	Idiopathic and hereditary PAH	Mutation frequency, clinical phenotype, prognosis	ACVRL1 variants represented a clinically relevant genetic subgroup with distinct prognostic implications.
Article 9	Longitudinal cohort study	Patients with genetically mediated PAH	ACVRL1 mutation carrier status	Heritable PAH	Disease progression, survival, therapeutic escalation	ACVRL1-positive cases showed faster progression and a greater need for advanced or combination therapy.
Article 10	Clinical genetics study	Patients with PAH and vascular malformation syndromes	ACVRL1 and ENG variants	HHT-related PAH	Clinical phenotype, bleeding manifestations, PH severity	ACVRL1-related disease was characterized by combined pulmonary vascular remodeling and systemic vascular manifestations.
Article 11	Observational cohort study	Pediatric and adult PAH patients	ACVRL1/ALK1 mutations	Early-onset and adult-onset PAH	Age at presentation, prognosis, clinical outcome	ACVRL1 mutations were particularly relevant in early-onset PAH and were associated with unfavorable prognostic features.

The figure 2 presents the methodological quality of the 11 included studies as assessed using the Newcastle-Ottawa Scale, which examines three core domains: selection, comparability, and outcome assessment. As individual study-level scores were not provided, the figure should be regarded as a provisional template for manuscript preparation. The final ratings should be updated based on full-text review before submission.

Study	Selection	Comparability	Outcome	Total NOS score
Article 1	To be rated	To be rated	To be rated	To be rated
Article 2	To be rated	To be rated	To be rated	To be rated
Article 3	To be rated	To be rated	To be rated	To be rated
Article 4	To be rated	To be rated	To be rated	To be rated
Article 5	To be rated	To be rated	To be rated	To be rated
Article 6	To be rated	To be rated	To be rated	To be rated
Article 7	To be rated	To be rated	To be rated	To be rated
Article 8	To be rated	To be rated	To be rated	To be rated
Article 9	To be rated	To be rated	To be rated	To be rated
Article 10	To be rated	To be rated	To be rated	To be rated
Article 11	To be rated	To be rated	To be rated	To be rated

NOS domains: Selection (maximum 4 stars), Comparability (maximum 2 stars), and Outcome (maximum 3 stars).
Suggested classification: high quality = 7–9 stars; moderate quality = 4–6 stars; low quality = 0–3 stars.

Figure 2. Methodological Quality Assessment of the 11 Included Studies According to the Newcastle-Ottawa Scale

Discussion

This systematic review provides a comprehensive synthesis of the prognostic landscape associated with ACVRL1/ALK1 mutations in pulmonary hypertension, underscoring a distinct clinical phenotype characterized by early disease onset and accelerated vascular deterioration. The collective findings from the 11 included studies indicate that pathogenic variants in ACVRL1 are robustly associated with worse hemodynamic profiles, including significantly elevated pulmonary arterial pressures and compromised right ventricular function, compared to non-carriers or those with other genetic predispositions. Furthermore, the evidence highlights a high rate of clinical progression and a disproportionate need for aggressive combination therapies or surgical interventions among ACVRL1 mutation carriers. These patients frequently demonstrate lower survival rates and higher hospitalization frequencies, particularly within the context of hereditary hemorrhagic telangiectasia-associated pulmonary arterial hypertension (HHT-PAH). Ultimately, the synthesis confirms that ACVRL1/ALK1 status serves as a critical prognostic determinant that can facilitate earlier risk stratification and more tailored therapeutic management in affected populations [10,11].

The aggressive clinical course observed in ACVRL1 mutation carriers can be fundamentally explained by the receptor's pivotal role in maintaining pulmonary endothelial quiescence and vascular structural integrity. Under physiological conditions, ALK1 acts as a high-affinity receptor for bone morphogenetic protein 9 (BMP9) and BMP10, triggering the phosphorylation of SMAD1/5/8 proteins that move to the nucleus to regulate genes essential for endothelial stability. When ACVRL1 is mutated, this homeostatic signaling is severely impaired, leading to a loss of growth control and a shift toward a pro-proliferative, anti-apoptotic endothelial environment. This molecular imbalance facilitates the rapid development of obstructive vascular lesions and plexiform structures, which are the hallmark of severe pulmonary arterial hypertension. The resulting increase in pulmonary vascular resistance occurs more rapidly and with greater intensity than in idiopathic cases, explaining why these patients present with more advanced disease at a younger age [12,13].

Another critical mechanism contributing to the poor prognosis in these patients is the induction of endothelial-to-mesenchymal transition (EndMT) resulting from deficient ALK1 signaling. In the absence of adequate ALK1-mediated Smad activation, pulmonary endothelial cells begin to lose their endothelial characteristics and acquire myofibroblast-like properties, contributing to excessive extracellular matrix deposition and medial hypertrophy. This transformation not only narrows the vascular lumen but also increases the stiffness of the pulmonary arteries, further exacerbating the

afterload on the right ventricle. Because EndMT is a self-sustaining and often irreversible process once initiated, its likely accounts for the suboptimal response to traditional vasodilators observed in this cohort. The recalcitrant nature of this remodeling process necessitates the early introduction of disease-modifying agents that target proliferative pathways rather than simple vasodilation [14,15].

The dual burden of systemic vascular malformations and pulmonary hypertension in patients with HHT Type 2 further complicates the prognostic profile and clinical outcomes. ACVRL1 is essential for systemic angiogenesis, and its mutation often leads to the development of arteriovenous malformations (AVMs) in the liver, lungs, and brain. Hepatic AVMs, in particular, can lead to high-output heart failure, which, when superimposed on pulmonary arterial hypertension, creates a complex hemodynamic state that rapidly exhausts cardiac reserves. This "double hit" on the right heart explains the higher rates of right ventricular failure and the earlier mortality reported in multicenter cohort studies. Clinicians must therefore manage these patients through a multidisciplinary approach that addresses both the pulmonary vascular resistance and the systemic shunting that characterizes the ACVRL1 genotype [16,17].

Furthermore, the severity of right ventricular (RV) dysfunction in ACVRL1-positive patients may be linked to the direct impact of ALK1 signaling on the cardiac endothelium and potentially the myocardium itself. While pulmonary hypertension is primarily a disease of the lung vasculature, the prognosis is ultimately determined by the ability of the right ventricle to adapt to increased afterload. Recent molecular evidence suggests that ALK1 may play a role in RV angiogenesis and capillary density; therefore, its deficiency might impair the compensatory hypertrophic response of the heart. This inadequate adaptation results in earlier RV-pulmonary arterial uncoupling, a physiological state that strongly correlates with clinical deterioration and sudden cardiac death. The inability of the heart to maintain adequate stroke volume in the face of rising resistance accounts for the poor functional class and reduced exercise tolerance identified as common themes in the reviewed literature [18,19].

The significant penetrance variations and the early onset of disease in pediatric populations suggest that ACVRL1 mutations may interact with secondary genetic modifiers or environmental triggers to dictate prognosis. Studies have shown that while some carriers remain asymptomatic, others develop life-threatening PAH in childhood, implying that the ACVRL1 pathway is highly sensitive to the broader genetic landscape, including variants in ENG or BMPR2. This genetic complexity likely explains the heterogeneity in survival outcomes observed across different families with the same mutation. The aggressive nature of the disease in younger carriers suggests that the ALK1-Smad pathway is particularly critical during the developmental phases of the pulmonary vasculature, where its absence leads to profound and rapid mal-development of the vascular bed. Consequently, genetic screening and longitudinal monitoring of at-risk relatives are essential for early intervention before irreversible remodeling occurs [20,21].

The prognostic utility of ACVRL1/ALK1 status is further reinforced by the observation that these patients often require earlier and more intensive escalations in therapy. Because the molecular drivers in these cases are so potent, monotherapy with endothelin receptor antagonists or PDE5 inhibitors is frequently insufficient to slow the progression of the disease. The data suggest that mutation carriers are more likely to undergo double or triple combination therapy and exhibit a shorter time-to-treatment-failure. This highlights the importance of using genetic status as a "red flag" to initiate more proactive management strategies, potentially including early referral for lung transplantation evaluation. Understanding the genetic underpinnings of the patient's disease allows for a shift from a reactive to a proactive clinical paradigm, where the aggressiveness of the treatment matches the underlying molecular severity [22,23].

The integration of ACVRL1 status into existing risk stratification models, such as the REVEAL score or the ESC/ERS guidelines, could significantly improve their predictive accuracy. Currently, these models rely heavily on clinical and hemodynamic parameters that may only become abnormal once significant damage has already occurred. By incorporating the ACVRL1 genotype which is a stable and early biomarker clinicians can identify "ultra-high-risk" individuals even when their initial hemodynamics appear relatively preserved. The association between ACVRL1 variants and unfavorable echocardiographic indices further supports the use of genotype-informed monitoring to detect early signs of RV strain. This personalized approach to risk assessment is essential for improving the long-term survival of patients who are genetically predisposed to a more virulent form of pulmonary hypertension [24,25].

Despite the clear prognostic signals, the heterogeneity in study designs and the rarity of the ACVRL1 genotype pose challenges for the universal standardization of clinical protocols. Many of the included studies were retrospective or involved small cohorts, which may introduce selection bias or limit the generalizability of the survival data. Additionally, the variable definitions of "prognosis" and "clinical outcome" across the literature ranging from hemodynamic stability to all-cause mortality

make it difficult to perform a precise meta-analysis of the effect size. However, the consistent direction of the findings across diverse geographic and clinical settings provides strong qualitative evidence for the negative prognostic impact of ACVRL1 mutations. Future prospective, multicenter registries with standardized genetic testing are needed to refine these prognostic estimates and develop genotype-specific therapeutic guidelines [26,27].

In conclusion, the prognostic role of ACVRL1/ALK1 in pulmonary hypertension is characterized by its association with a severe, early-onset, and rapidly progressive clinical phenotype. The underlying molecular pathology involves a catastrophic failure of endothelial signaling, leading to profound vascular remodeling and early cardiac decompensation. The identification of ACVRL1 mutations should be considered a critical event in the diagnostic workup, as it provides invaluable information regarding the patient's expected clinical trajectory and response to therapy. By acknowledging the specific challenges faced by this genetic subgroup, the medical community can move closer to achieving the goals of precision medicine in the management of pulmonary vascular disease. Ultimately, the use of ALK1 as a prognostic biomarker offers the best opportunity for early intervention and improved clinical outcomes in this high-risk population [28,29].

Conclusion

ACVRL1/ALK1 mutations serve as a critical prognostic biomarker in pulmonary hypertension, identifying a high-risk cohort characterized by early-onset disease and rapid hemodynamic deterioration. Incorporating ACVRL1 genotyping into clinical risk stratification is essential for optimizing surveillance and initiating aggressive, personalized therapeutic interventions. Future prospective multicenter trials are necessary to refine genotype-specific survival estimates and standardize long-term management protocols for this vulnerable patient population.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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