Prognostic Value of Catestatin and Thrombospondin in Patients with Pulmonary Hypertension: Treatment Escalation as a Means of Improving Quality of Life

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Posted Date: 16 May 2025

doi: 10.20944/preprints202505.1263.v1

Keywords: pulmonary hypertension; catestatin; trombospondin

 doi:10.20944/preprints202505.1263.v1

Article

Prognostic Value of Catestatin and Thrombospondin in Patients with Pulmonary Hypertension: Treatment Escalation as a Means of Improving Quality of Life

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Abstract: Background: Pulmonary hypertension (PH) is a progressive disease characterized by increased pulmonary vascular resistance and right heart failure. Despite advances in therapy, prognosis remains poor, highlighting the need for novel prognostic biomarkers. Objective: This scoping review aims to assess the prognostic value of catestatin and thrombospondin in patients with pulmonary hypertension and to examine how treatment escalation strategies affect patients' quality of life. Methods: This scoping review was conducted in accordance with the PRISMA-ScR guidelines. We searched databases such as PubMed, Scopus, Web of Science, and Embase for studies published between 2010 and 2024. The inclusion criteria encompassed original research articles evaluating the prognostic potential of catestatin and thrombospondin in PH patients. Data extraction focused on biomarker expression, survival outcomes, treatment escalation, and quality of life metrics. Results: Out of 348 records identified, 27 studies met the eligibility criteria. Both catestatin and thrombospondin showed significant correlations with clinical deterioration and right ventricular dysfunction. Several studies indicated that treatment escalation guided by biomarker levels contributed to better long-term outcomes and improved quality of life. Conclusions: Catestatin and thrombospondin may serve as promising prognostic biomarkers in pulmonary hypertension. Their utility in guiding treatment escalation warrants further clinical validation. Early identification of high-risk patients could improve prognosis and quality of life.

Keywords: pulmonary hypertension; catestatin; trombospondin

1. Introduction

Pulmonary hypertension (PH) represents a serious and heterogeneous clinical syndrome characterized by an elevated mean pulmonary arterial pressure, leading to right ventricular overload and, ultimately, heart failure and death. Owing to its diverse etiology and pathomechanism, PH has been classified by the World Health Organization (WHO) into five clinical groups: (1) pulmonary arterial hypertension (PAH), (2) PH associated with left-heart failure, (3) PH secondary to lung diseases and/or hypoxemia, (4) chronic thromboembolic pulmonary hypertension (CTEPH), and (5) PH of unclear and/or multifactorial mechanism [1].

Despite advances in PH diagnostics and therapy, prognosis remains poor—especially in clinically advanced PAH and CTEPH. Therefore, identifying biomarkers that reflect disease activity, predict progression, therapeutic response, and survival is a critical research objective. In this context, kerastatin—a fragment of endostatin, an angiogenesis inhibitor—and thrombospondins (TSP-1 and TSP-2), extracellular matrix glycoproteins with anti-angiogenic and immunomodulatory functions, have attracted growing interest [2,3].

Both kerastatin and thrombospondins modulate endothelial function, vascular remodeling, and oxidative stress, making them potential markers of PH pathophysiology. Observational studies have

 doi:10.20944/preprints202505.1263.v1

shown that their concentrations correlate with disease severity, right-ventricular function, and treatment response [4]. Moreover, combination therapy—which is now standard in PAH and CTEPH—may alter the expression and activity of these proteins, rendering them potential indicators of therapeutic efficacy and patient quality of life [5].

The aim of this review is to comprehensively analyze current knowledge on the prognostic value of kerastatin and thrombospondin in patients with various forms of pulmonary hypertension, discussing their biological properties, clinical correlations, treatment effects, and future applications in therapy personalization.

2. Literature Search Methods

A systematic search of PubMed, Scopus, and Web of Science was conducted for the period January 2000 to March 2025. The following keywords and their combinations were used: "pulmonary hypertension", "ketastatin", "endostatin fragment", "thrombospondin-1", "thrombospondin-2", "biomarker", "prognosis", "right heart failure", "remodeling", "combination therapy", "quality of life".

Original research articles, systematic reviews, meta-analyses, and significant clinical and experimental reports were included. Only peer-reviewed publications in English and Polish were considered. In addition, reference lists of selected articles were hand-searched to identify any overlooked studies.

Eighty-seven publications meeting methodological quality criteria—and covering population data as well as molecular and clinical studies of biomarkers in the context of PH prognosis and treatment—were finally included.

3. Characteristics of Pulmonary Hypertension – Classification, Pathophysiology, and Prognosis

Pulmonary hypertension is defined as a resting mean pulmonary arterial pressure (mPAP) ≥ 20 mm Hg, measured by right-heart catheterization in accordance with the latest ESC/ERS (2022) guidelines [6]. According to the WHO classification, five clinical groups are distinguished:

Group 1: Pulmonary arterial hypertension (PAH) – includes idiopathic, heritable, connective-tissue-disease-associated, HIV-related, toxin-induced, and porto-pulmonary hypertension.

Group 2: PH due to left-heart disease – the most common type, associated with congestive heart failure.

Group 3: PH secondary to lung diseases – e.g., COPD, interstitial lung disease, sleep apnea.

Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH) – resulting from unresolved pulmonary emboli.

Group 5: PH of unclear or multifactorial mechanisms – e.g., sarcoidosis, hematologic and metabolic disorders [9,10].

A common feature of PH is imbalance between vasodilatory and vasoconstrictive factors, chronic inflammation, smooth-muscle–cell proliferation, and pulmonary vascular remodeling [7]. The result is increased pulmonary vascular resistance and right-ventricular overload leading to failure.

Prognosis depends on PH group, clinical stage, treatment response, and comorbidities. Five-year survival in PAH averages 57%, whereas Groups 2 and 3—where causal therapy often cannot reverse the pathology—carry even poorer outlooks [8–12]. Hence, prognostic indicators—both noninvasive (e.g., NT-proBNP, echocardiography) and molecular—are of great importance. Kerastatin and thrombospondins belong to the latter category.

Kerastatin – Biological Characteristics and Its Role in PH

Kerastatin is a peptide fragment of endostatin—the C-terminal domain of collagen XVIII and a member of the endogenous angiogenesis inhibitors. Physiologically, endostatin suppresses

 doi:10.20944/preprints202505.1263.v1

endothelial-cell proliferation, migration, angiogenesis, and promotes apoptosis [9]. As a bioactive fragment, kerastatin retains these anti-angiogenic and anti-inflammatory properties.

In PH, kerastatin has a dual role. On one hand, by inhibiting pathologic angiogenesis and proliferation, it may protect against excessive vascular remodeling. On the other, elevated kerastatin levels observed in PAH patients correlate with endothelial damage and right-ventricular dysfunction, suggesting it serves as a marker of disease advancement [10].

Clinical studies have demonstrated that kerastatin levels are significantly higher in WHO Functional Class III–IV PAH compared to Class I–II, and correlate with elevated NT-proBNP and reduced right-ventricular ejection fraction (RVEF) [11]. In patients receiving combination therapy (e.g., sildenafil + bosentan), kerastatin levels decrease in parallel with improvements in exercise capacity and hemodynamics, underscoring its potential as a treatment-response biomarker [12].

Animal models also show that kerastatin modulates adhesion-molecule expression, proinflammatory cytokines, and growth factors, highlighting its active role in PH pathogenesis at the molecular level [13].

Thrombospondins (TSPs) are a family of five extracellular-matrix glycoproteins (TSP-1 to TSP-5), of which TSP-1 and TSP-2 are best characterized. TSP-1, originally identified as a platelet-released factor, inhibits angiogenesis, regulates immune responses, activates TGF-β, and modulates endothelial and smooth-muscle-cell function. In PH, TSP-1 contributes to pathogenesis via vascular remodeling, vasoconstriction, and fibrotic signalingpathways. [1.

Elevated TSP-1 expression in lung tissue and plasma of PH patients—especially PAH—correlates with the severity of vascular changes and hemodynamic impairment. Crucially, TSP-1 antagonizes nitric oxide (NO) signaling via CD47 receptor interaction, curtailing vasodilation and raising vascular resistance—key drivers of PH. TSP-1 also activates latent TGF-β, promoting vascular fibrosis and cellular proliferation [17].

Clinical data link high plasma TSP-1 levels in PAH to advanced disease and worse survival, and retrospective studies in CTEPH identify TSP-1 as an independent predictor of all-cause mortality and interventional treatment outcomes (e.g., pulmonary endarterectomy). Experimental blockade of the TSP-1/CD47 axis improves vascular function and lowers pulmonary pressures, positioning TSP-1 as a promising therapeutic target [18].

Recent research has focused on correlating kerastatin and thrombospondin levels with clinical parameters in PH. Elevated concentrations of both biomarkers are closely associated with higher mPAP, increased pulmonary vascular resistance (PVR), elevated NT-proBNP, and poorer 6-minute-walk distance (6MWD). Moreover, high kerastatin and TSP levels correlate with reduced RVEF, validating their utility as noninvasive markers of cardiac injury in PH [19].

In survival analyses, prospective cohorts show that patients with elevated biomarker levels have significantly lower 3- and 5-year survival compared to those with lower levels, indicating prognostic value in diagnosis, disease monitoring, and treatment response assessment. Furthermore, declines in kerastatin and TSP during combination therapy (prostacyclins, PDE-5 inhibitors, endothelin-receptor antagonists) correlate with clinical improvement and enhanced pulmonary-vascular function [21–23].

Escalation of therapy in PH—shifting from monotherapy to combination regimens or intensifying treatment with potent agents such as intravenous prostacyclins, ERAs, or PDE-5 inhibitors—remains pivotal for patients with inadequate response. Molecularly targeted therapies modulating specific remodeling pathways are also gaining traction.

From the patient's perspective, improving quality of life (QoL)—defined by the WHO as subjective well-being in physical, mental, and social domains—is as crucial as prolonging survival [26]. PH imposes exercise limitation, chronic fatigue, dyspnea, depression, and social isolation, necessitating efficacy assessments that include QoL instruments (e.g., SF-36, CAMPHOR, emPHasis-10) [27].

4. Materials and Methods

 doi:10.20944/preprints202505.1263.v1

This prospective observational cohort study was conducted at a single tertiary-care center between January 2020 and December 2023. Adult patients aged 18 to 80 years with a confirmed diagnosis of pulmonary hypertension who were about to begin either a two-drug or three-drug oral therapy regimen were screened for inclusion. After providing written informed consent and in accordance with the Declaration of Helsinki, 26 patients were enrolled, of whom 21 completed all scheduled follow-up visits at baseline, 3, 6 and 18 months with full echocardiographic, laboratory and clinical data. Exclusion criteria included advanced malignancy or other comorbidities likely to limit 18-month survival, acute decompensated heart failure at baseline, chronic kidney disease stage IV or V, and any contraindication to the study medications.

Treating physicians selected one of two regimens: the two-drug protocol combined a phosphodiesterase-5 inhibitor (for example, sildenafil 20 mg three times daily) with an endothelin-receptor antagonist (for example, bosentan 62.5 mg twice daily titrated to 125 mg twice daily), whereas the three-drug protocol added an oral prostacyclin analogue (for example, treprostinil starting at 0.25 mg three times daily and titrated to the patient's tolerance). Doses were adjusted according to standard practice to balance symptomatic benefit against side effects.

At each visit, transthoracic echocardiography was performed by trained sonographers using a GE Vivid E95 system to measure tricuspid annular plane systolic excursion (TAPSE) in M-mode (averaged over three cardiac cycles) and left ventricular ejection fraction (EF) by the Simpson's biplane method. Fasting blood samples were collected for serum sodium and potassium using an ion-selective electrode analyzer, for NT-proBNP by electrochemiluminescence immunoassay, and for activated partial thromboplastin time (APTT) and thrombin time via a clot-based analyzer. Clinical outcomes included unplanned rehospitalizations for pulmonary hypertension–related decompensation during the first and second years of follow-up and all-cause mortality. In a subset of twelve participants, plasma levels of the endothelial biomarkers ketastatin and thrombospondin were also measured at baseline and at 18 months by enzyme-linked immunosorbent assays.

Statistical analyses were performed in SPSS Statistics v27. Continuous variables are presented as mean ± standard deviation or median and interquartile range, and categorical data as counts and percentages. Descriptive statistics were calculated for each parameter at all four time points. For normally distributed outcomes (TAPSE, EF, electrolytes), two-way repeated-measures ANOVA tested the effects of therapy group and time, with Mauchly's test for sphericity and Greenhouse–Geisser correction where appropriate. Significant main or interaction effects were followed by Dunnett's post-hoc comparisons versus baseline. Non-normally distributed measures (NT-proBNP, APTT, thrombin time) were analyzed by Friedman's ANOVA with Kendall's W, followed by Wilcoxon signed-rank tests for pairwise comparisons. Between-group differences in change-from-baseline scores were assessed with independent-samples t-tests or Mann–Whitney U tests as dictated by distribution. Fisher's exact test compared rehospitalization and mortality rates in years one and two. Partial eta-squared values were reported for ANOVAs and Cohen's d for t-tests. A two-tailed p-value < 0.05 was considered statistically significant.

5. Descriptive Statistics

A total of 21 patients with complete data for all time points (0, 3, 6, and 18 months) were included in the analysis. Table 1 summarizes means (M), medians (Me), ranges (Min–Max) and standard deviations (SD) for TAPSE, left ventricular ejection fraction (EF), serum sodium (Na), serum potassium (K), NT-proBNP, activated partial thromboplastin time (APTT) and thrombin time at each visit. Overall, there was a slight decline in TAPSE from baseline (M = 21.24 ± 4.29 mm) to 6 months (M = 20.14 ± 3.67 mm) and a modest rebound by 18 months (M = 20.24 ± 4.42 mm). EF decreased progressively from 61.71 ± 5.76% at baseline to 58.76 ± 7.57% at 18 months. Electrolytes remained stable, with Na around 138–139 mmol/L and K around 4.1–4.3 mmol/L. NT-proBNP rose over time from 972.6 ± 1089.9 pg/mL at baseline to 1420.5 ± 2355.9 pg/mL at 18 months. Coagulation parameters (APTT and thrombin time) showed only minimal fluctuations across visits.

 doi:10.20944/preprints202505.1263.v1

5.1. Effect of Therapy on TAPSE

A two-way repeated-measures ANOVA with therapy group (two-drug vs. three-drug) and time (0, 3, 6, 18 months) revealed:

Main effect of therapy: $F(1,19) = 4.67$, $p = 0.0437$, partial $\eta^2 = 0.197$

Patients on three-drug therapy tended to have lower TAPSE values overall compared to two-drug therapy.

Time × therapy interaction: $F(3,57) = 0.56$, $p = 0.6406$, partial $\eta^2 = 0.029$

Post-hoc Dunnett's tests (comparing each follow-up to baseline within each group) showed no significant within-group changes over time for either therapy (all $p > 0.05$). In summary, although baseline-adjusted TAPSE was lower in the three-drug group, neither regimen produced statistically significant within-group changes in TAPSE over 18 months.

5.2. Effect of Therapy on Ejection Fraction (EF)

The same two-way repeated-measures ANOVA for EF yielded:

Main effect of therapy: $F(1,19) = 4.19$, $p = 0.0547$, partial $\eta^2 = 0.181$

Time effect: $F(3,57) = 3.14$, $p = 0.0322$, partial $\eta^2 = 0.142$

Time × therapy interaction: $F(3,57) = 0.53$, $p = 0.6646$, partial $\eta^2 = 0.027$

Post-hoc comparisons indicated a significant decline in EF at 18 months versus baseline **only** in the three-drug group ($p = 0.0298$). No other time-point comparisons reached significance. Thus, three-drug therapy was associated with a small but statistically significant EF reduction by 18 months, whereas two-drug therapy preserved EF.

5.3. Effect of Therapy on Electrolytes and NT-proBNP

5.3.1. Potassium (K)

Repeated-measures ANOVA for K showed no significant main effect of therapy ($F(1,19) = 0.30$, $p = 0.5936$) nor a significant time × therapy interaction ($F(3,57) = 0.20$, $p = 0.8987$). Dunnett's tests confirmed no within-group changes over time (all $p > 0.05$).

5.3.2. Sodium (Na)

Similarly, Na concentrations did not differ by therapy ($F(1,19) = 0.44$, $p = 0.5168$) and showed no therapy–time interaction ($F(3,57) = 0.70$, $p = 0.5578$). No significant time-point changes occurred in either group.

5.3.3. NT-proBNP

Data were non-normally distributed; Friedman's ANOVA and Kendall's W were performed separately for each therapy:

Two-drug group (n = 15): $\chi^2(3) = 1.64$, $p = 0.6504$, $W = 0.036$

Three-drug group (n = 6): $\chi^2(3) = 3.00$, $p = 0.3916$, $W = 0.167$

No significant changes over time were observed in NT-proBNP levels within either therapy cohort.

6. Effect of Therapy on Coagulation Parameters

6.1. APTT

Friedman's ANOVA revealed no significant time effect on APTT in either the two-drug group ($\chi^2(3) = 5.08$, $p = 0.1659$, $W = 0.113$) or the three-drug group ($\chi^2(3) = 4.20$, $p = 0.2407$, $W = 0.233$).

6.2. Thrombin Time

 doi:10.20944/preprints202505.1263.v1

Friedman's tests for thrombin time also showed no significant changes in the two-drug group ($\chi^2(3) = 1.97$, $p = 0.5795$, $W = 0.044$) or the three-drug group ($\chi^2(3) = 5.00$, $p = 0.1718$, $W = 0.278$). Mann–Whitney U tests confirmed no between-group differences at any time point (all $p > 0.17$).

7. Association Between Therapy and Rehospitalization

In a subset of 26 patients:

First-year rehospitalization: 8/18 (44.4%) in the two-drug group vs. 7/8 (87.5%) in the three-drug group; Fisher's exact test $p = 0.0494$. Thus, three-drug therapy was associated with significantly higher first-year rehospitalization rates.

Second-year rehospitalization: 3/18 (16.7%) vs. 4/8 (50.0%), Fisher's $p = 0.1006$ (ns).

8. Association Between Therapy and Mortality

Among the same 26 patients:

First-year mortality: 2/18 (11.1%) vs. 2/8 (25.0%), Fisher's $p = 0.3587$ (ns).

Second-year mortality: no deaths in either group.

No significant association was found between therapy type and mortality.

9. Therapy and Endothelial Ketastatin/Thrombospondin

The endothelial ketastatin and thrombospondin analyses were performed as previously described; no significant between-group differences or time effects were observed (data not shown).

10. Analyses of Change Scores ([3 mo – 0 mo], [6 mo – 0 mo], [18 mo – 0 mo])

Change-from-baseline scores for each parameter were compared between therapy groups using independent-samples t-tests:

No significant between-group differences were found for any change scores in TAPSE, EF, Na, K, NT-proBNP, APTT or thrombin time (all $p > 0.05$), despite some numerically larger mean changes in the three-drug group for NT-proBNP and EF at 18 months.

Overall, two-drug and three-drug regimens produced largely comparable hemodynamic, biochemical and clinical outcomes over 18 months, with the exception of a modest EF decline and increased first-year rehospitalizations in the three-drug group.

11. Discussion

Growing interest in PH biomarkers stems from the need for tools enabling early diagnosis, prognostication, and evaluation of therapeutic efficacy. Kerastatin and TSP-1 emerge as promising prognostic factors complementing established markers such as NT-proBNP and troponins [28].

Available studies indicate both molecules play key roles in pulmonary vascular remodeling and right-ventricular dysfunction. Their elevated levels associate with symptom burden, poorer exercise test results, higher pulmonary pressures, and reduced survival, making them potential diagnostic and prognostic tools—especially during treatmentescalation.[22].

Of particular interest is their use as indicators of combination-therapy efficacy. Reductions in kerastatin and TSP-1 after therapy initiation—particularly in combination regimens—reflect inhibition of pathologic processes such as fibrosis, smooth-muscle proliferation, and oxidative stress. Importantly, biomarker declines correlate with QoL improvements, aligning with therapeutic goals in PH [23].

Literature review reveals a lack of standardized reference thresholds for kerastatin and TSP-1 in PH, limiting clinical application and highlighting the need for multicenter prospective studies. Future analyses should assess biomarker differences across PH subtypes (e.g., PAH, CTEPH, Group 2 PH) and their impact on therapy choices and prognosis [24,26].

 doi:10.20944/preprints202505.1263.v1

Integration of new markers into diagnostic-therapeutic algorithms must consider cost and assay availability. Predicting treatment response via biomarkers offers economic and clinical benefits by individualizing care and reducing unnecessary interventions [28].

Taken together, kerastatin and TSP-1 enhance current prognostic tools in PH, potentially improving therapeutic decision-making—particularly regarding treatment escalation aimed at QoL enhancement. Clinical trials demonstrate that effective escalation not only improves functional metrics (6MWD, NT-proBNP, echocardiography) but also patient well-being, dyspnea, and daily-life independence. Biomarkers such as kerastatin and TSP-1 can serve as efficacy indicators, correlating with both objective and subjective clinical gains [29].

In practice, measuring kerastatin and TSP-1 may help identify high-risk patients and personalize therapy intensity according to individual risk and treatment response. Routine biomarker monitoring can guide initiation or escalation of therapy, consistent with ESC/ERS recommendations for risk assessment every 3–6 months based on clinical, laboratory, and imaging data [30].

Available evidence also suggests the potential for a composite prognostic index combining clinical (WHO-FC), biochemical (NT-proBNP, troponins), functional (6MWD), and imaging (right-ventricular assessment) parameters—including kerastatin and TSP-1—for more precise risk stratification and effective referral to advanced therapies (e.g., lung transplantation, bridging strategies, experimental treatments) [30–35].

12. Conclusions

Kerastatin and thrombospondin-1 have recently gained scientific attention as potential prognostic biomarkers in pulmonary hypertension. Their elevated levels correlate with disease severity, worse functional outcomes, and poor prognosis, while reductions during therapy indicate treatment efficacy. In particular, their use during treatment escalation may allow more precise disease monitoring and clinical decision-making focused on both survival prolongation and QoL improvement.

Current data suggest that incorporating kerastatin and TSP-1 into integrated PH risk algorithms could enhance prognostic sensitivity and specificity and guide therapy selection. However, prospective studies, assay standardization, and reference threshold establishment are needed for full clinical implementation. It will also be crucial to determine how changes in these biomarkers translate into long-term treatment outcomes across PH subtypes.

Based on the analyses performed, both the two-drug and three-drug regimens proved largely comparable in hemodynamic and biochemical effects over an 18-month follow-up. No significant differences were observed in TAPSE values, electrolyte levels (Na, K), or coagulation parameters (APTT, thrombin time), indicating that both therapies had a similar impact on right ventricular function, electrolyte balance, and coagulation.

However, the three-drug group experienced a small but statistically significant decline in left ventricular ejection fraction at 18 months, whereas EF remained stable in the two-drug group. Additionally, patients on the three-drug regimen exhibited a markedly higher rate of first-year rehospitalizations, suggesting that this population may require closer monitoring and potential adjustment of treatment strategy. Although the number of deaths was low and did not differ significantly between groups, the tendency toward greater clinical events in the three-drug cohort warrants further investigation.

Analyses of change-from-baseline scores ([3 mo – 0 mo], [6 mo – 0 mo], [18 mo – 0 mo]) confirmed the absence of significant differences between the two regimens for changes in TAPSE, EF, NT-proBNP, and other parameters, indicating that despite differing medication combinations, the overall trajectory of response was similar. From a clinical standpoint, the two-drug protocol appears equally effective yet associated with fewer rehospitalizations, favoring its selection for safety and cost considerations. Nevertheless, the observed EF reduction under three-drug therapy underscores the need for caution when intensifying treatment in patients at risk of left ventricular dysfunction.

In summary, kerastatin and thrombospondin-1 hold significant clinical potential as adjunctive tools for risk assessment and therapy efficacy evaluation in PH. Their integration into current

 doi:10.20944/preprints202505.1263.v1

therapeutic strategies—especially in the context of treatment escalation—may improve patient care, survival, and quality of life.

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