Article type: Rapid Communication
Home Page URL: https://www.alliedacademies.org/journal-cancer-clinical-research/

Fibrosis-Related Biomarkers in Cardiovascular Medicine: Pathophysiological and Prognostic Significance of Galectin-3 and ST2.

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Received: *27-May-2025, Manuscript No. AACCR-25-169796;* ***Editor assigned:*** *01-Jun-2025, PreQC No. AACCR-25-169796 (PQ);* ***Reviewed:*** *15- Jun-2025, QC No. AACCR-25-169796;* ***Revised:*** *22- Jun-2025, Manuscript No. AACCR-25-169796 (R);* ***Published:*** *29- Jun-2025, DOI:10.35841/AATCC-8.1.184*

Introduction

Fibrosis, the aberrant deposition of extracellular matrix components, is a hallmark of chronic pathological remodeling in numerous organ systems, including the heart, liver, lungs, and kidneys. In cardiovascular disease, particularly heart failure, fibrosis plays a pivotal role in disease progression, symptom exacerbation, and poor clinical outcomes. Among the array of molecular mediators and indicators of fibrosis, two biomarkers—Galectin-3 and ST2—have emerged as particularly valuable in both research and clinical domains. These biomarkers offer insights into the underlying pathophysiological mechanisms of cardiac remodeling and carry prognostic relevance across a spectrum of cardiovascular conditions.Galectin-3, a β-galactoside-binding lectin secreted primarily by activated macrophages, has been identified as a critical modulator of fibrogenesis. Through its ability to activate fibroblasts and stimulate the production of collagen and other extracellular matrix proteins, Galectin-3 serves as both an effector and a marker of fibrotic processes. Elevated plasma concentrations of Galectin-3 have been associated with worse outcomes in patients with heart failure, particularly those with preserved ejection fraction (HFpEF), where fibrosis is believed to play a more prominent role compared to heart failure with reduced ejection fraction (HFrEF).

Moreover, Galectin-3 is not confined to cardiac-specific pathology. It is increasingly recognized in systemic fibrotic disorders, suggesting a broader utility in identifying fibrotic burden across different organ systems. The U.S. Food and Drug Administration has approved Galectin-3 as a biomarker for use in heart failure risk stratification, underscoring its clinical significance. Nevertheless, its specificity remains a matter of concern, as Galectin-3 levels can be influenced by other conditions such as renal dysfunction, inflammation, and malignancy.On the other hand, suppression of tumorigenicity 2 (ST2), particularly its soluble isoform sST2, is a member of the interleukin-1 receptor family and functions as a decoy receptor for interleukin-33 (IL-33). The IL-33/ST2 signaling pathway is protective in the setting of cardiac stress, exerting anti-hypertrophic and anti-fibrotic effects. However, when sST2 is elevated in circulation, it sequesters IL-33 and disrupts this beneficial signaling, thus facilitating pathological remodeling and fibrosis. sST2 is a highly dynamic biomarker that responds to myocardial strain and inflammation, making it particularly useful in acute and chronic heart failure. In contrast to natriuretic peptides, sST2 is less affected by factors such as age, obesity, and renal function, which enhances its utility in diverse patient populations. The prognostic value of sST2 in heart failure has been well established, with higher levels predicting mortality and hospitalization independently of other biomarkers. Furthermore, serial measurements of sST2 have been proposed as a strategy for monitoring therapeutic response and adjusting treatment plans, although this practice is still under evaluation in clinical trials.

The combined assessment of Galectin-3 and sST2 may offer additive prognostic value, given their representation of different yet interrelated aspects of cardiac fibrosis and inflammation. While Galectin-3 primarily reflects fibrogenic activation through macrophage-fibroblast crosstalk, sST2 highlights biomechanical stress and the suppression of reparative signaling. Together, they provide a more nuanced picture of cardiac remodeling than either biomarker alone. Several clinical studies

have supported the complementary nature of these biomarkers in predicting adverse outcomes in heart failure and other cardiovascular diseases, including myocardial infarction and atrial fibrillation. Despite their promise, limitations remain. The variability in assay standardization, cutoff thresholds, and the influence of comorbidities can hinder their widespread clinical adoption. Moreover, it is yet to be fully determined whether targeting Galectin-3 or sST2 directly through pharmacological interventions would confer therapeutic benefit. Initial research into Galectin-3 inhibitors and modulators of IL-33/ST2 signaling is underway, but these efforts are still in the early stages of development.

Beyond their role in diagnostics and prognostics, Galectin-3 and sST2 are valuable research tools for understanding the molecular basis of fibrosis. Their involvement in immune cell recruitment, fibroblast activation, and tissue remodeling provides insight into the complex network of cellular interactions that drive fibrotic diseases. Animal models and human tissue studies have illustrated how these biomarkers are upregulated in response to myocardial injury and contribute to sustained tissue damage when unchecked. By integrating molecular biology with clinical cardiology, these findings may pave the way for personalized medicine approaches where biomarker profiling guides treatment decisions and risk stratification.

Emerging technologies such as high-throughput proteomics, transcriptomics, and single-cell RNA sequencing are expected to further unravel the regulatory networks surrounding Galectin-3 and sST2. These technologies will allow researchers to identify upstream regulators and downstream effectors, providing additional targets for therapeutic intervention. Moreover, as the field of precision medicine evolves, these biomarkers may be incorporated into multifactorial risk models that account for genetic, proteomic, and clinical parameters. Such comprehensive models could significantly enhance our ability to predict disease progression and response to therapy, particularly in complex syndromes like heart failure and systemic fibrotic disorders.

Conclusion

Fibrosis is a fundamental pathological process that underlies the progression of various chronic diseases, particularly in the cardiovascular system. Galectin-3 and sST2 serve as important biomarkers that offer insights into the complex biology of fibrosis and hold significant prognostic value. As our understanding of these biomarkers deepens, they may become indispensable tools in the clinical management of heart failure and beyond. With further validation and refinement, Galectin-3 and sST2 have the potential to enhance diagnostic precision, guide therapy, and ultimately improve patient outcomes in fibrotic cardiovascular diseases.

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Citation: Kirtane A. Fibrosis-Related Biomarkers in Cardiovascular Medicine: Pathophysiological and Prognostic Significance of Galectin-3 and ST2. J Can Clinical Res. 2025; 8(1):184