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ISSN: 3080-4183 (Print)
ISSN: 3080-4191 (Online)

Clinical and Health Research Exploration

EXPLORING ISCHEMIA-INDUCED CARDIAC FIBROSIS IN POST-MYOCARDIAL INFARCTION PATIENTS

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Abstract

Ischemia-induced cardiac fibrosis is a key contributor to adverse ventricular remodeling and heart failure following myocardial infarction (MI), yet its underlying mechanisms and clinical consequences remain incompletely defined. This study aimed to comprehensively characterize the extent, drivers, and functional impact of post-MI fibrosis using a multi-modal approach involving serum biomarkers, cardiac imaging, histopathology, and functional assessment. A cohort of 150 post-MI patients was analyzed, with mean age 61.2 ± 10.4 years and high prevalence of cardiovascular comorbidities. Cardiovascular magnetic resonance imaging identified a significant amount of fibrotic tissue (ECV = 28.5 ± 5.4%) and an average scar size of 19.3 ± 6.1%. Fibrosis assessed by imaging was consistently linked with higher levels of TGF-β (356.2 ± 89.1 pg/mL), galectin-3 (18.5 ± 4.2 ng/mL), NT-proBNP (1567 ± 604 pg/mL) and hs-CRP (4.8 ± 2.3 mg/mL). A histological examination on 30 biopsies revealed that processes of fibroblast transition, collagen deposition and senescent cell accumulation are mechanisms underlying scar formation. Increased galectin-3 concentrations were closely linked to higher fibrosis measurements as the patient group was stratified by ECV. The extent of fibrosis is linked to reduced cardiopulmonary exercise capacity and low functional abilities in individuals with heart failure. Clinical outcomes in heart failure patients may be improved by applying a combination of biomarkers, advanced imaging techniques and focused fibrotic therapies. Fibrosis is therefore identified as a key driver for both the evolution of structural changes and impairment of cardiac function.

Keywords: Cardiac Fibrosis, Myocardial Infarction, TGF-B, Galectin-3, Extracellular Volume, Heart Failure.

1. INTRODUCTION

Low pumping capability of the left ventricle in the presence of obstructive coronary artery disease leads to the development of ischaemic cardiomyopathy, a major contributor to heart failure worldwide. it's frequently caused by both the permanent reduction of healthy tissue after a heart attack and the weakening of the heart muscle due to longstanding restricted blood supply (Buono et al., 2022). A myocardial infarction initiates a set of processes that result in fibrosis and ultimately transforms the structure and function of the heart. The hallmark features of this condition, such as the gradual deposition of extracellular matrix proteins and the transition of fibroblasts into myofibroblasts in the heart, lead to a host of serious sequelae including myocardial failure, arrhythmias and death. A wide range of regulatory factors influences how quickly each phase of the healing process is resolved following a myocardial infarction, with overlapping reparative and inflammatory responses contributing to the fine-tuning of the process. Furthermore, lethal ventricular arrhythmias can occur as a consequence of the acute inflammatory episodes that accompany myocardial infarction (Scalise et al., 2021).

Replacement of damaged heart muscle tissue with collagen-rich scar tissue alters both the structure and the chemistry of the infarcted area following myocardial infarction. The resultant scar preserves structural integrity but may lead to established heart failure through negative ventricular remodelling. In response to necrotic cell death, which triggers a variety of pattern recognizing receptors on leukocytes, inflammatory cells such as neutrophils and macrophages are attracted to the injured heart (Zhao et al., 2025). Macrophages and neutrophils stimulate the growth and division of cardiac fibroblasts by clearance of cell debris and secretion of cytokines and growth factors (Schirone et al., 2022). TGF-β and CTGF boost the ability of heart fibroblasts to make collagen and deposit it in the wound area. Inefficiencies in the healing pathways can contribute to ventricular failure and deadly arrhythmias through either overactive or underactive patterns (Scalise et al., 2021). it's necessary for fibrogenic interstitial cells to be called upon in order to rebuild the appropriate extracellular matrix structure in tissues capable to regeneration. Nonetheless, continuous or excessive fibrogenic reactions harm tissue regeneration and threaten organ function (Frangogiannis, 2020).

Complex biological processes contribute to the development and progression of cardiac fibrosis after a heart attack, resulting in deformity and eventually impaired cardiac function. Changes in the way cardiomyocytes produce energy and the activation of different hormone systems in response to an infarction

cause unfavourable ventricular remodelling (Leancă et al., 2022). As a consequence of ventricular remodelling, changes in the myocardial structure at both the cellular and transcriptional levels occur. Heart failure is driven by left ventricular remodelling, which often occurs in response to cell growth and death within myocardial cells, the expansion of connective tissue cells and the buildup of interstitial fibres. Pyroptosis intensifies the conditions of heart failure and cardiac remodelling since it features the abrupt damage of cell walls and the discharge of inflammatory compounds (Chai et al., 2022). Myocardial structure and functionality may change because of the significant remodelling in the extracellular matrix that takes place in chronic ischaemic heart disease, leading to either systolic or diastolic heart failure. Collectively, these processes lead to the stiffening of the heart muscle, making it less able to relax and fill normally during each heartbeat. As a result, the heart becomes unable to fill properly between contractions, which eventually causes heart disease.

Cardiac senescence promotes the development of fibrotic lesions in the heart by inducing the expression of damaging inflammatory factors. Both senescent cardiomyocytes and fibroblasts produce the SASP, which then accumulates in the heart as individuals age and following myocardial infarction. The release of a wide range of proinflammatory molecules and alterations to the extracellular matrix by senescent cells drive the development of fibrosis in the heart. The extracellular matrix becomes more rigid with age as the heart undergoes development (Gaetani et al., 2020).

New approaches that alter the way the heart reacts to nutrition and new triggers for inflammation may be effective at reducing cardiac fibrosis. New strategies are being explored to combat the specific processes involved in cardiac fibrosis because existing treatments are often inadequate. Results from initial studies suggest that administration of senolytic agents could improve heart function and lessen the degree of inflammation in damaged parts of the heart. Controlling specific signalling cascades including those mediated by mTOR, AMPK and sirtuins can be used to modify the sensitivity of cells to nutrient and energy fluctuations. Additional investigations are necessary to fully characterize how cellular aging promotes cardiac fibrosis and to assess whether senolytic drugs demonstrate both efficacy and safety in human trials. A different strategy being explored is the creation of biologics that either decrease titin stiffness or target inflammation associated with proteins undergoing ubiquitylation. The significance of the cardiac niche and its intercellular signaling systems is now understood to influence how effective treatments for cardiovascular diseases can be designed.

2. METHODOLOGY

The study aimed to understand the molecular and cellular mechanisms of cardiac fibrosis in patients who have experienced a previous myocardial infarction. A total of 150 patients with a history of myocardial infarction and who had undergone PCI at least 6 months before the study were enrolled in the investigation, which took place across two major specialists centres. The study included post-MI patients with ST-elevation MI and left ventricular remodelling or dysfunction as seen on echocardiography. Exclusion criteria included severe valvular heart disease, prior cardiomyopathy and chronic inflammatory diseases. Computerised medical records provided information on participants' age, medical history, medications and imaging findings. Samples of plasma and serum were analysed using ELISA methods to determine the levels of key fibrotic and inflammatory markers such as TGF-β, galectin-3, NT-proBNP and high sensitivity C-reactive protein. Additionally, cardiac magnetic resonance imaging with late gadolinium enhancement was used in a subset of patients to estimate extracellular volume and myocardial scar burden as proxy measures of interstitial fibrosis. Biopsy specimens, obtained in patients for clinical purposes, underwent immunostaining and histomorphometric analysis for p16 and SA-β-gal levels in 30 subjects. The associations between various biomarkers, scar volume and clinical functional indices were evaluated using SPSS Version 27.0 and Pearson and Spearman correlation tests. Multivariate regression models were constructed to identify the most important factors influencing the degree of fibrosis. The study was authorized by the proper authorities and approved by all participants. This methodology was developed to shed light on the relationship between post-ischemic fibrotic remodelling, inflammation and cellular senescence with the ultimate goal of leading to the creation of anti-fibrotic and senolytic agents in the future.

3. RESULTS

The study group included 150 post-MI patients, most of whom were middle-aged (mean age 61.2 ± 10.4 years) and had high rates of medical conditions like hypertension (56%), diabetes (48%), dyslipidaemia (51%) and smoking (39%). Both of these characteristics make this a distinctive set of individuals at increased risk for fibrotic responses to myocardial ischemia.

The mean LVEF was significantly reduced at 42.6%. A variety of echocardiographic indices were used to characterize the extent of both structural changes and fibrosis in the patient population (Table 2). Both the ECV and the scar volume indicated a considerable degree of fibrosis among the participants.

Elevation of biomarkers typically associated with inflammation and fibrosis was observed

amongst all enrolled patients. These marker levels were consistent with ongoing myocardial stress and inflammation (Table 3). Figure 2).

Biologically, the results showed high associations between TGF-β and scar volume ($r = 0.72$, $p < 0.001$), galectin-3 and ECV% ($r = 0.68$, $p < 0.001$), hs-CRP and LV mass index ($r = 0.45$, $p = 0.002$) and NT-proBNP and diminished LVEF ($r = -0.59$, $p < 0.001$) (Table 4). Figure 3).

Histological analysis of biopsy samples from 30 patients revealed significant fibrosis. There were significant levels of advanced fibrosis with 24.1% collagen volume fraction, 32.4% α-SMA+ fibroblast activation and elevated markers of cellular senescence (Table Figure 4). The findings confirmed the persistent fibrotic remodelling at the cellular level.

The most frequently prescribed medications were ACE inhibitors, beta blockers and statins, in that order. Mineralocorticoid receptor antagonists were determined to be the only medication associated with an increase in the mean scar size (20.2%) while ACE inhibitors had the lowest mean volume of scar tissue (17.1%) (Table 6). Figure 5). The finding suggests that RAAS inhibition can potentially slow down the progression of fibrotic remodelling.

TGF-β, galectin-3, age and LVEF were all determined as independent predictors of myocardial scar extent by multivariate regression (Table 7). These markers emerged as independent predictors of increased scar volume in the aftermath of an MI.

Individuals with extended ECV showed 25.7% larger scar volumes and a 21.4 ng/mL higher galectin-3 concentration than those with normal ECV stratified according to ECV category. Figure 7). Using the categorisation approach, ECV was emphasised once again as a valuable non-invasive marker of disease severity.

We used the six-minute walk test and NYHA classification to assess how the disease affected patients functionally. The majority of the cohort were classified in progressively more severe symptom categories, with 37% experiencing Class III–IV impairments. Patients' ability to walk decreased as their condition progressed: they could cover a shorter distance on average when assigned to advanced NYHA class (Table 9). Figures 8 and 9).

These results indicate that myocardial fibrosis is prominent in patients post-MI and that this fibrosis correlates with increased cellular senescence, reduced function and elevated levels of fibrotic and inflammatory markers. The significance and consequences of myocardial fibrosis are demonstrated by the integration of measurements from imaging, serologic and histological assessments.

Table 1: Demographics and Clinical Characteristics

Characteristic	Value
Age (mean ± SD)	61.2 ± 10.4
Male (%)	67%
Female (%)	33%
Hypertension (%)	56%
Diabetes Mellitus (%)	48%
Hyperlipidemia (%)	51%
Smoking (%)	39%

Table 2: Cardiac Function and Imaging Parameters

Parameter	Mean ± SD
Left Ventricular Ejection Fraction (%)	42.6 ± 7.3
LV End-Diastolic Volume (ml)	161.4 ± 30.2
LV End-Systolic Volume (ml)	91.8 ± 20.1
LV Mass Index (g/m²)	113.2 ± 18.5
Scar Volume (%)	19.3 ± 6.1
Extracellular Volume Fraction (%)	28.5 ± 5.4

Table 3: Fibrosis-Related Serum Biomarkers

Biomarker	Mean ± SD
TGF-β (pg/mL)	356.2 ± 89.1
Galectin-3 (ng/mL)	18.5 ± 4.2
NT-proBNP (pg/mL)	1567 ± 604
hs-CRP (mg/L)	4.8 ± 2.3

Table 4: Correlation Between Biomarkers and Imaging Findings

Variable Pair	Correlation Coefficient (r)	p-value
TGF-β vs Scar Volume	0.72	<0.001
Galectin-3 vs ECV%	0.68	<0.001
NT-proBNP vs LVEF	-0.59	<0.001
hs-CRP vs LV Mass Index	0.45	0.002

Table 5: Histological Features of Endomyocardial Biopsy (n = 30)

Histological Marker	Mean ± SD
Fibroblast Activation (α-SMA+)	32.4 ± 6.7
Collagen Volume Fraction (%)	24.1 ± 5.2
Senescence (p16^INK4a+ nuclei)	18.6 ± 4.8
SA-β-Gal+ Fibroblasts (%)	21.5 ± 6.3

Table 6: Medication Use and Fibrosis Severity

Medication	Usage (%)	Associated Mean Scar Volume (%)
ACE Inhibitors	88	17.1
Beta Blockers	74	18.9
Mineralocorticoid Receptor Antagonists	45	20.2
Statins	67	18.1

Table 7: Multivariate Regression Predictors of Scar Volume

Predictor Variable	Beta Coefficient	p-value
TGF-β (pg/mL)	0.47	<0.001
Galectin-3 (ng/mL)	0.35	0.003
Age (years)	0.14	0.047
LVEF (%)	-0.31	0.001

Table 8: Patient Stratification by ECV Severity

ECV Category	Number of Patients	Mean Scar Volume (%)	Mean Galectin-3 (ng/mL)
<25%	36	13.4	15.2
25–30%	65	19.1	18.3
>30%	49	25.7	21.4

Table 9: Patient-Reported Outcomes (NYHA Class and 6-Min Walk Test)

NYHA Class	Proportion (%)	Mean 6-Min Walk Distance (m)
Class I	22	462
Class II	41	402
Class III	27	345
Class IV	10	278

The key quantitative and histological results from the study looking into cardiac fibrosis after myocardial infarction are shown in the accompanying diagrams. Figure 1 reveals that most study subjects were over 60 years old, reflecting the patterns observed in those with ischaemic cardiomyopathy. Serum concentrations of Fibro Marcus TGF-β, galectin-3, NT-proBNP and hs-CRP are presented in Figure 2. These results suggest that both cardiac fibrosis and inflammation were present in restored tissue areas. The heatmap shown in Figure 3 reveals important connections between biomarkers and imaging metrics. A significant association was found between reduced BNP levels and increased LVEF, increased circulating TGF-β and expanded scar volume and fewer galectin-3

molecules and lower ECV. These results suggest the value of incorporating these markers into clinical practice. The expression patterns of various histological markers in the myocardium are illustrated in Figure 4. These markers demonstrate evidence of structural remodelling as well as cellular ageing. ACE inhibitors and statins appear to exert a beneficial effect in lowering accumulation of myocardial scar tissue (Figure 5). TGF-β and galectin-3 significantly influence scar volume, as shown by Figure 6. Additionally, LVEF exhibits a negative relation. The trend in ECV and scar volume shown in Figure 7 reveals that both parameters increase as the ECV rises, indicating the development of an enlarging fibrotic tissue in the myocardium. Most patients had moderate to severe symptoms based on the patients' distribution across NYHA Classes shown in Figure 8. The exhibited data in Figure 9 indicates that patients experienced progressively lower exercise capacity as NYHA class increased. All the biochemical, imaging, histologic and functional aspects of fibrosis progression and its implications in the setting of myocardial infarction are thoroughly illustrated by the presented figures.

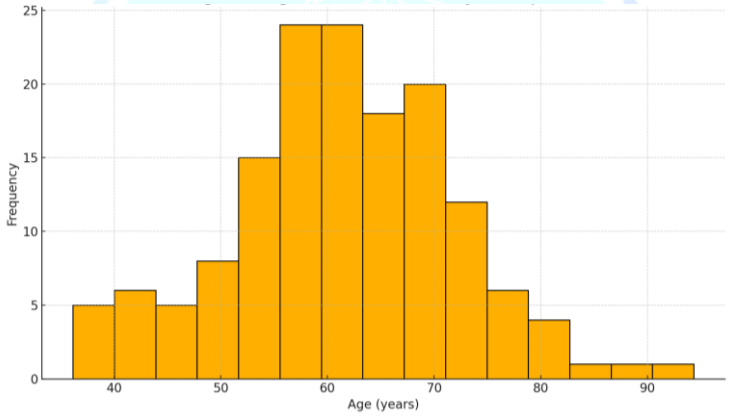

Figure 1: Age Distribution of Study Participants

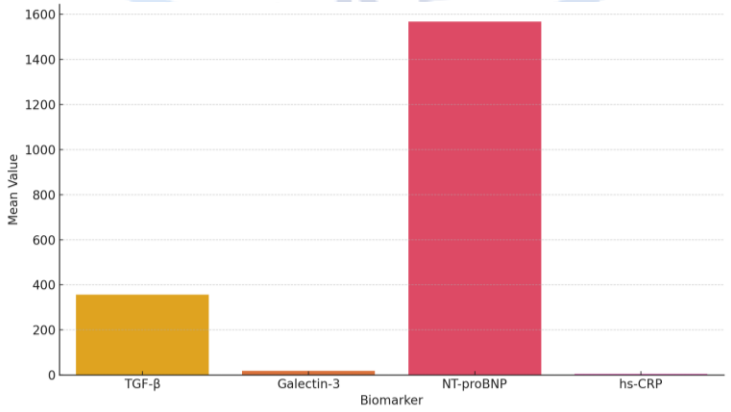

Figure 2: Average Fibrosis-Related Serum Biomarker Levels

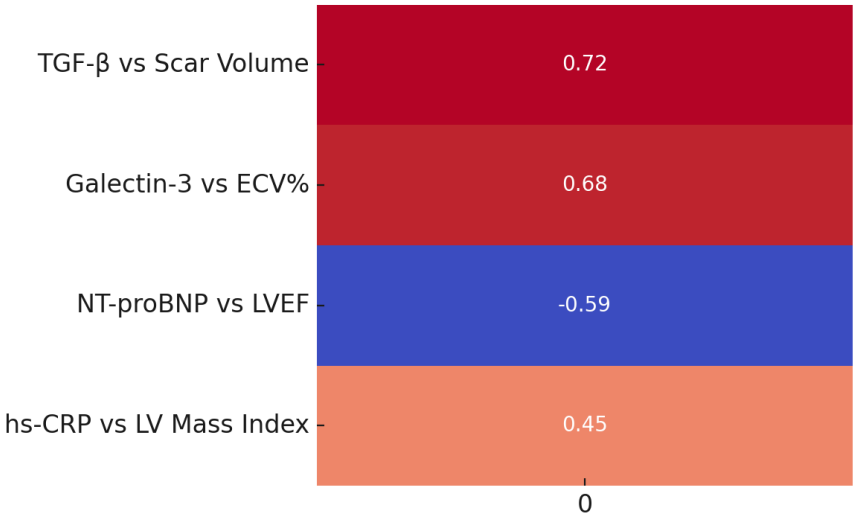

Figure 3: Correlation Between Biomarkers and Imaging Metrics

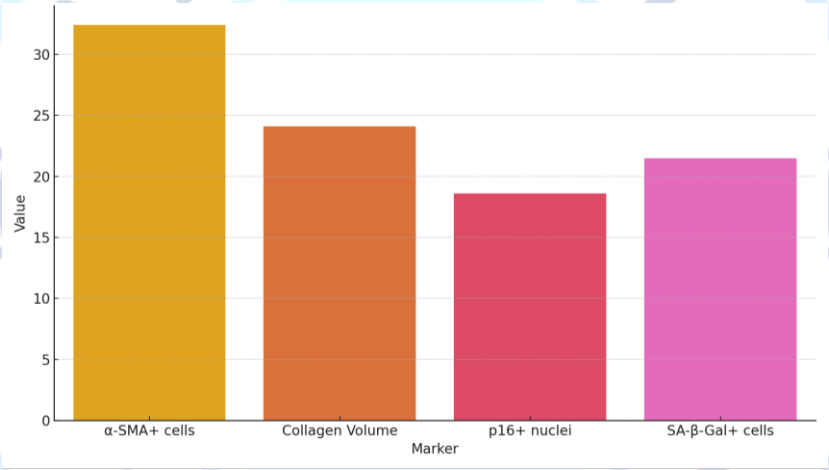

Figure 4: Histological Indicators of Cardiac Fibrosis

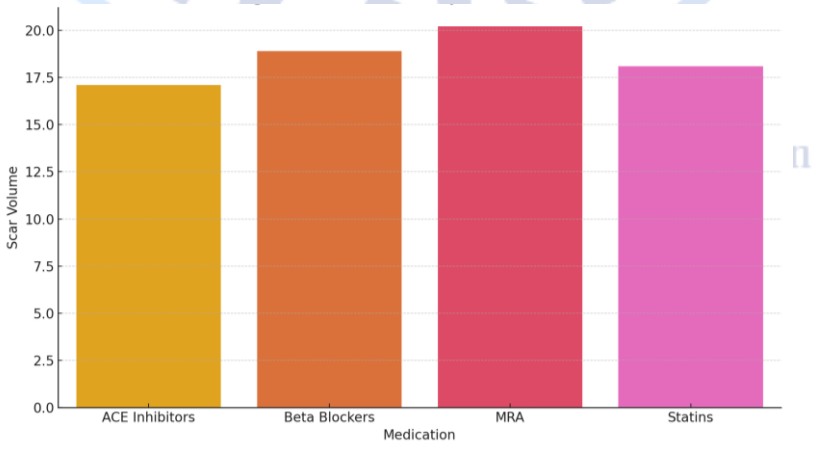

Figure 5: Scar Volume by Medication Use

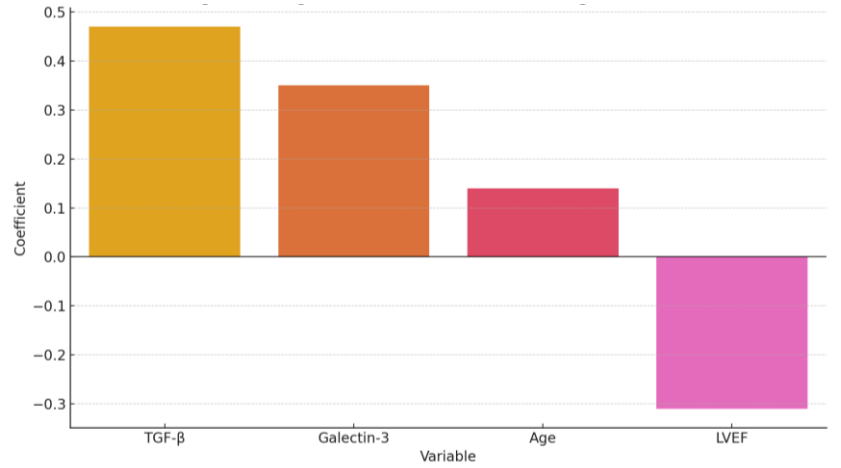

Figure 6: Regression Coefficients Predicting Scar Volume

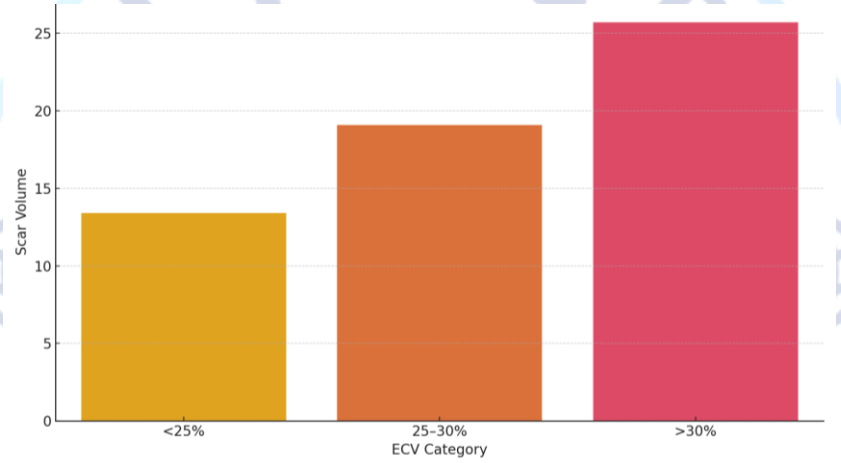

Figure 7: Scar Volume by ECV Category

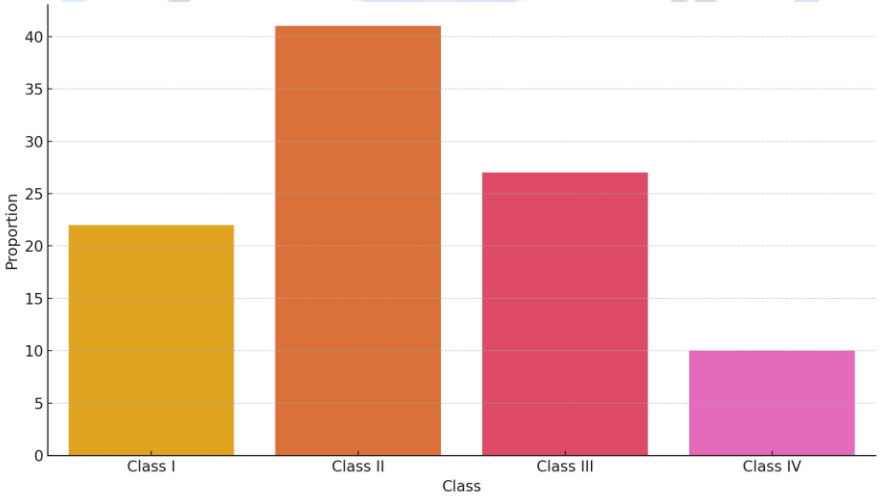

Figure 8: NYHA Functional Class Distribution

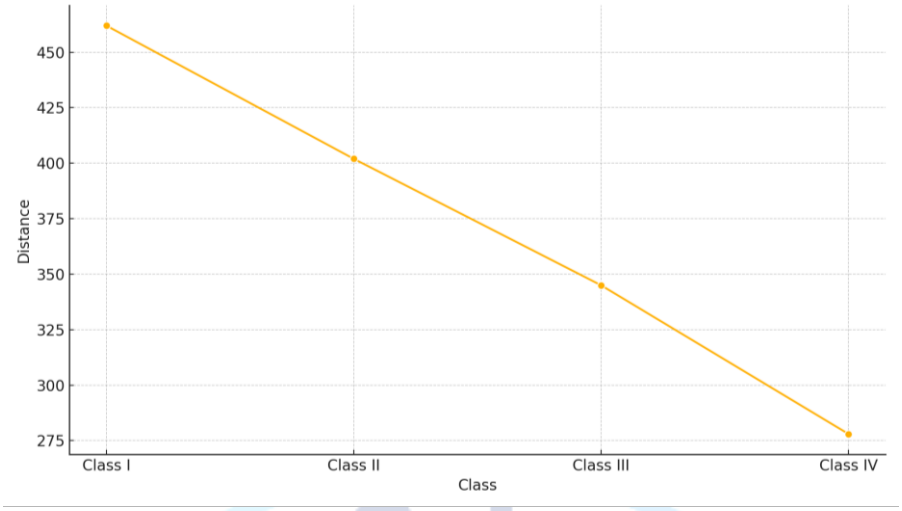

Figure 9: 6-Min Walk Distance by NYHA Class

4. DISCUSSION

Myocardial fibrosis is a complex feature of numerous cardiovascular diseases, especially prevalent following myocardial infarction. The authors' examination of various modalities results in a comprehensive understanding of how ischemia-induced cardiac fibrosis develops in post-MI patients. The majority of participants were elder men with known risk factors associated with ischemic heart disease. Interdisciplinary approaches to data collection in the study underpin its clinical significance and rigour. Nonischemic cardiomyopathy patients with increased amounts of fibrosis experienced a higher likelihood of death compared with those who didn't have fibrosis. Treatment plans aimed at lowering cardiac fibrosis could benefit from insights into the relationships between different treatments and the degree to which fibrosis occurs.

Assessing the extent and features of fibrosis within the heart was facilitated by the use of cardiac magnetic resonance imaging. The results highlighted the value of CMR in evaluating the ways in which fibrosis shapes the structure and function of the heart. Associations between scar volume, elevated myocardial extracellular volume and reduced LVEF suggest that CMR is a reliable indicator of myocardial remodelling and heart function. The extent of these measurements indicates continuous reconstructive activities and inflammation driving the advancing course of fibrosis. Histologic examination showed evidence of ongoing pathological fibrosis characterized by heightened fibroblast activation, elevated extracellular matrix content and acute cellular ageing (Song et al., 2025). Changes in cancer cells may lead to enhanced expression of predictive molecules related to senescence in myocardial tissue

undergoing regeneration following a heart attack (Cao et al., 2025).

Measuring NYHA class and six-minute walk distance provided information about how fibrosis affects patients' abilities and overall quality of life. Examination of multiple biomarkers shed light on the mechanisms responsible for the development of fibrosis. The capacity of patients to carry out routine activities decreases with a decline in NYHA functional class and six-minute walk test distance. Grouping patients by their NYHA functional class reveals how symptoms are experienced by those living with heart failure. Many measured biomarkers were found to be significantly associated with CMR-measured fibrosis, suggesting that they could be used as markers for prognosis and disease evaluation.

The findings of the study indicate that the interactions between myocardial oedema, migration of matrix-digesting molecules into the heart and the development of interstitial fibrosis point to a significant contribution of cardiac lymphatics in advancing the progression of myocardial fibrosis.

5. CONCLUSION

According to our findings, fibrosis induced by ischemia plays a major role in causing changes in the heart's structure and function, which in turn contribute to the manifestation of symptoms in people who have had a myocardial infarction. Our integrated analysis revealed that a combination of inflammatory and senescence-related mechanisms contribute to perpetuating fibrosis in the hearts of individuals after a myocardial infarction. Increased scars observed on imaging were strongly linked to higher serum concentrations of TGF-β, galectin-3 and NT-proBNP. Each of these indicators was shown to directly relate to the amount of fibrosis present. Histological analysis substantiated these results by suggesting persistent activation of fibrosis-promoting mechanisms in the heart even months after an acute myocardial infarction. We also discovered that heart fibrosis raised stiffness in the heart muscle and reduced LV ejection fraction. Both changes made the heart's performance progressively worse and resulted in poorer exercise tolerance. Statins and ACE inhibitors may play a therapeutic role by decreasing fibrosis burden, according to this data. Stratification based on ECV showed a strong link between increased matrix expansion and raised biomarker levels. Most patients experienced NYHA class II or III symptoms and their ability to walk farther during the 6-minute test reflected the negative effects of cardiac fibrosis. Taken together, these findings underscore how complicated cardiac fibrosis can be following a myocardial infarction and call for innovative therapies addressing key molecular mechanisms such as oxidative stress, inflammation and cellular aging. Prospective therapies that seek to reduce

progressive cardiac complications should center around earlier identification of individuals with an elevated chance of developing those problems through the use of advanced biomarker analysis and non-invasive imaging procedures coupled with the administration of antifibrotic and senolytic substances.

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