Review

Myocardial fibrosis and viability: the role of imaging and biomarkers in patients with chronic total occlusion on coronary angiography

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Highlights

- Viable myocardium guides treatment decisions in chronic coronary disease
- Early detection of myocardial fibrosis may improve patient outcomes
- Terminal collagen propeptides are promising markers of myocardial fibrosis
- Galectin-3 links inflammation and fibrosis in the myocardium
- Identifying reliable fibrosis biomarkers could enhance viability assessment

Abstract

In patients with chronic total occlusion on coronary angiography, myocardial viability assessment is an essential tool in guiding treatment decisions, especially revascularization. Current non-invasive tests are often limited by the presence of myocardial fibrosis. This narrative review incorporates evidence from 76 studies and aims to provide an updated overview of non-invasive methods for myocardial viability assessment, with emphasis on the role of myocardial fibrosis. Every imaging modality provides valuable information, even though they differ in sensitivity, specificity, availability, radiation exposure, contraindications and limitations in the presence of fibrosis. Biomarkers that provide insight into different aspects of myocardial fibrosis – including collagen synthesis (procollagen type I carboxy-terminal propeptide and procollagen type III amino-terminal propeptide), as well as inflammation and fibrotic signalling (galectin-3) – may complement imaging by reflecting myocardial remodelling. However, main limitations to this approach are no standardized reference ranges and cut-off values, analytical variability and insufficient validation for clinical outcomes prediction. Despite their potential to guide personalized revascularization decisions, circulating fibrosis biomarkers currently remain experimental tools. Further large-scale prospective clinical studies that incorporate biomarkers with imaging are needed before their implementation into clinical practice.

Keywords: biomarkers; collagen; coronary artery disease; fibrosis; galectin 3

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Introduction

Chronic total occlusion (CTO) is defined by the CTO Academic Research Consortium as major coronary artery occlusion without forward flow that has been present for ≥ 3 months (1). It is found in 15-20% of patients undergoing coronary angiography (2,3). Although collateral circulation devel-

ops to compensate for reduced blood flow, it is often insufficient to fully restore myocardial perfusion (4).

The rate and severity of complications for percutaneous coronary intervention in patients with CTO are higher (1-3%) when compared to other procedures in chronic coronary syndrome (3,5-7). However, performing percutaneous coronary intervention in patients with symptoms (angina or dyspnoea) significantly improves their quality of life compared to optimal medical therapy (8-11).

On the other hand, treatment decisions in asymptomatic patients rely on accurate myocardial viability assessment, which can predict functional recovery after revascularization (12,13). Non-invasive imaging modalities used for myocardial viability assessment differ in specificity, sensitivity, availability, operator-dependence and radiation exposure (14,15). Their diagnostic accuracy may also be complicated by the presence of myocardial fibrosis (16).

Circulating fibrosis biomarkers – procollagen type I carboxy-terminal propeptide (PICP), procollagen type III amino-terminal propeptide (PIIINP) and galectin-3 (Gal-3) – show promising results in viability assessment by reflecting direct tissue remodelling. They have the potential to identify fibrotic non-viable myocardium earlier and more precisely (17,18).

The aim of this review is to summarize current non-invasive imaging modalities for myocardial viability assessment, explain the pathophysiological role of myocardial fibrosis and evaluate circulating fibrosis biomarkers as complementary tools for clinical decision-making for revascularization in patients with CTO.

Methods

This paper is a structured narrative review. A literature search was conducted and finished in May 2025 to identify publications relevant to the role of non-invasive imaging and circulating biomarkers (particularly PICP, PIIINP and Gal-3) in myocardial viability and fibrosis. The search covered publications from January 2005 to May 2025. It was performed using the PubMed/MEDLINE database because it provided the most comprehensive and peer-reviewed indexed sources in imaging and biomarker research relevant to CTO population. Non-indexed databases were excluded to improve clinical relevance and minimize heterogeneity. The following keywords and their combinations using Boolean operators (AND, OR) were used to refine the search: "myocardial viability", "fibrosis biomarkers", "myocardial fibrosis", "imaging", "chronic coronary syndrome", "chronic total occlusion", "PICP", "PIIINP", and "Galectin-3". Titles/abstracts and full texts were screened by two independent reviewers, with disagreements resolved by a senior third reviewer.

Inclusion criteria:

- Original research papers, meta-analyses, systematic reviews or guidelines
- Studies including adult patients (> 18 years of age) with coronary artery disease, chronic coronary syndrome or heart failure with fibrosis related aetiology
- Animal studies that provide insights relevant to fibrosis or myocardial viability
- Studies evaluating non-invasive myocardial viability assessment and pathophysiology of myocardial fibrosis that are relevant to circulating fibrosis biomarkers (PICP, PIIINP, Gal-3).

Exclusion criteria:

- Non-English articles
- Case reports, editorials and conference abstracts
- Pediatric or congenital heart disease population
- Animal studies without relevance to fibrosis or myocardial viability.

After screening for eligibility, 76 studies were included as follows: 13 covering chronic total occlusion, 14 myocardial viability imaging modalities, 11 pathophysiology of myocardial fibrosis, 15 collagen biomarkers and 23 galectin-3. The study selection process is shown in Figure 1.

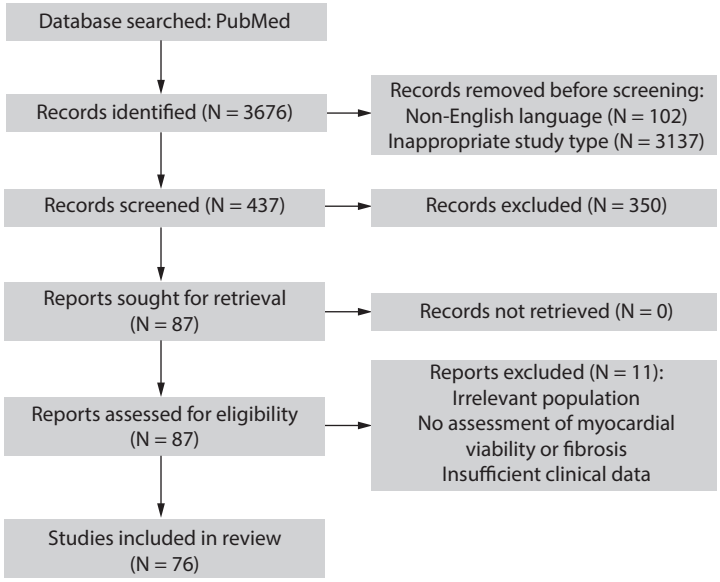

Figure 1. PRISMA-style flow diagram of the literature search and study selection process

Myocardial viability testing

In research and clinical practice, viable myocardium shows contractile cellular dysfunction at rest, which is expected to improve after coronary revascularization. Recurrent ischemia triggers myocardial hibernation – adaptive down-regulation of myocardial function – which exists on a clinical spectrum of reversible ischemic dysfunction (19). Myocardial stunning represents impaired contractility following resolution of acute ischemia, lasting for several hours or days, but recovering spontaneously (20). Both hibernating and stunned myocardium are considered viable. Viability should be considered as a spectrum, where revascularization of each component may yield diverse pathophysiological benefits (19).

The utility of a viability test is judged on its accurate prediction of contractile dysfunction reversal after revascularization using quantitative and/or qualitative measures. Improvement may occur within hours to days in areas of stunned myocardium, or months in areas of hibernating myocardium. Every imaging method focuses on a different element of pathophysiology (21). Viability imaging modalities differ in their advantages and limitations (Table 1), but they all play an essential role in the management of patients with chronic coronary syndrome and CTO. The choice should be individualized based on patient characteristics, possible contraindications, expertise and local availability (22).

Positron emission tomography (PET) assesses glucose metabolism using glucose analogues, where preserved glucose uptake indicates viable myocardium even when contractility is impaired. It demonstrates the highest sensitivity for detecting preserved metabolic activity and predicting contractile recovery. However, its accuracy depends on standardized preparations (fasting, glycemic control and insulin protocols) and does not directly quantify the scar tissue, which may lead to false positive results in acutely stunned or inflamed myocardium (23-26).

Single photon emission computed tomography (SPECT) evaluates regional blood flow by quantifying intracellular uptake of perfusion tracers (*e.g.*, 99mTc-sestamibi). It is widely used due to its accessibility and familiarity, even though its lower spatial resolution and reduced accuracy in comparison to PET limits its use for detailed viability characterization (27,28).

Table 1. Comparison of non-invasive imaging modalities for viable myocardium detection

Test	Advantages	Disadvantages
SPECT	• Inexpensive • Widely available	• Exposure to radiation • False negatives in the setting of multi-vessel disease • False positives due to attenuation
PET	• Greater accuracy than SPECT • Anatomical information	• Exposure to radiation • Limited availability and facility expertise
DSE	• No exposure to radiation or contrast • Structural information • Higher specificity in obese and female patients	• Dependant on technical expertise and imaging quality • Lower sensitivity in the setting of single-vessel disease
CMR	• Higher sensitivity and specificity • Gives detailed structural information	• Expensive, limited availability • Contraindicated in advanced renal disease • Affected by presence of arrythmia

*Adapted from (20). SPECT - single photon emission computed tomography. PET - positron emission tomography. DSE - dobutamine stress echocardiography. CMR - cardiac magnetic resonance.

Dobutamine stress echocardiography (DSE) assesses contractile reserve by stimulating β1-adrenergic receptors with dobutamine, causing systolic thickening in viable myocardium. It has high specificity for predicting short and mid-term functional improvement after revascularization. However, image quality and interpretability depend on the acoustic window and operator expertise, which may reduce diagnostic accuracy (15).

Cardiac magnetic resonance (CMR) evaluates myocardial tissue using late gadolinium enhancement for scar quantification and quantitative mapping (native T1 and extracellular volume) for measurement of diffuse interstitial fibrosis. It provides the most comprehensive structural assessment, but its use may be limited due to availability, as well as in patients with renal dysfunction and implanted devices (29,30).

A perfect method for myocardial viability testing has not been found. Fibrotic tissue, which results from chronic damage and remodelling, may not accurately reflect the true viability of the heart muscle. This can lead to challenges in distinguishing viable and non-viable tissue, influencing treatment plans. Therefore, it is important to understand the pathophysiology of myocardial fibrosis.

Myocardial fibrosis

Myocardial fibrosis represents a significant global health problem implicated in nearly all forms of heart disease leading to increased left ventricular stiffness and impaired contraction and relaxation (31,32). It develops when persistent injury, such as chronic ischemia, pressure overload or neurohormonal activation, triggers sustained inflammatory and pro-fibrotic signalling (33).

The fibrotic response can be divided into three phases: the initiative, the effective and the amplificative phase (34). Sustained activation by mechanical stress stimulates the production of circulating and myocardial cytokines and pro-fibrotic growth factors which (in the effective phase) bind to their receptors triggering the activation of transcriptional factors and signalling pathways resulting in the transformation of cardiac fibroblasts into myofibroblasts (35). Activated myofibroblasts synthesize excess collagen type I and III and expand the extracellular matrix (ECM) (21,36).

There are three main patterns of myocardial fibrosis – replacement, reactive interstitial and perivascular (Table 2). Replacement fibrosis reflects irreversible scarring after cardiomyocyte loss, while reactive interstitial and perivascular fibrosis repre-

Table 2. Types of myocardial fibrosis

Type of fibrosis	Characteristics	Common cause	Functional impact
Replacement	Collagen scar formation replacing cardiomyocytes Usually reparative and protective*	Myocardial infarction	Systolic dysfunction
Reactive interstitial	ECM accumulation without cardiomyocyte loss	Chronic activation of pro-fibrotic stimuli Hypertension, obesity, diabetes mellitus Microvascular dysfunction	Diastolic dysfunction Reduced left ventricular compliance Impaired myocardial perfusion
Perivascular	Expansion of microvascular adventitia		

*Replacement fibrosis has a critical protective role by ensuring the structural integrity of the heart and preventing mechanical complications after myocardial infarction (37). ECM - extracellular matrix.

sent diffuse remodelling that progresses despite preserved cardiomyocyte viability. Extensive fibrosis reduces the nutrient supply to the cardiomyocytes creating a vicious cycle of inflammation, cell death and ECM expansion (37).

These tissue-level changes have an impact on diagnostic testing. Expansion of the ECM increases the distribution volume for gadolinium, affecting late gadolinium enhancement patterns and T1 extracellular volume mapping on CMR (29,30). Reduction of capillary density and alteration of mitochondrial function may impact tracer uptake in nuclear perfusion imaging, lowering the accuracy of PET and SPECT for viability assessment (28). Similarly, myocardial fibrosis limits contractile reserve, diminishing the sensitivity of DSE for identifying the potential for functional recovery (15).

Given the clinical significance of myocardial fibrosis, early detection and monitoring of its progression are crucial for improving patient outcomes. Circulating biomarkers of collagen turnover, fibrotic signalling and inflammation may serve as complementary tools and provide insight into myocardial remodelling.

Biomarkers of myocardial fibrosis

Circulating biomarkers, detected in blood or urine, should ideally reflect the underlying pathophysiological processes in the target conditions or organs (33). The investigation of myocardial fibrosis biomarkers has received increasing attention in research communities. They are often molecules that play an essential part in the complex process of fibrosis development (38). Endomyocardial biopsy with quantification of collagen volume fraction by histology remains the gold standard for the diagnosis and staging of myocardial fibrosis. However, it is an invasive procedure with a risk of sampling error which limits its use to selected patients and research settings (39). This highlights the need for non-invasive imaging and circulating fibrosis biomarkers.

Collagen synthesis biomarkers

As previously mentioned, myocardial fibrosis represents abnormal distribution and deposition of collagen, mainly increased collagen deposition and collagen turnover. Procollagen type I and III propeptides are markers of its synthesis and breakdown (38).

The ECM in the heart is composed predominantly of collagen type I (85%) and III (11%). They are both synthetized by cardiac fibroblasts as fibrillar collagen or procollagen, which is then split by proteinases in carboxy (C) and amino (N) terminal propeptides (40). Procollagen type I carboxy-terminal propeptide and procollagen type III amino-terminal propeptide are currently the only proven circulating peptides associated with proven myocardial interstitial fibrosis on endomyocardial biopsy (41).

Collagen type I is a fibrillar protein, aligned in fibres, present in almost all connective tissue structures, including bones, tendons, skin, sclera, blood vessels, as well as in other tissues providing a structural matrix. The dominant isoform is heterotrimer consisting of two α1 (I) and one α2 (I) chain (17). Its synthesis may be directly reflected by plasma concentrations of PICP because it is produced by cleavage in a ratio of 1:1 (42). On the other hand, PIIINP plasma concentrations may not be an accurate marker of collagen synthesis due to its smaller size, even though it has been linked to the amount of collagen type III fibres in the myocardium of heart failure patients (43).

Collagen type III is responsible for myocardial elasticity in reticular fibres in interstitial tissue of the heart, liver, lung and blood vessels. It is a homotrimer consisting of three α1 (III) chains overlapped in a triple helix (17). After proteases cleave propeptides of fibrillar collagen, PIIINP is released into the bloodstream by the lymphatics. It is considered to have an important role in fibril diameter, as well as having great storage capacity and stability (42).

A variety of immunoassay-based techniques are used to measure PICP and PIIINP, including enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIA), and electrochemiluminescence immunoassays (ECLIA). However, there is considerable analytical variability between platforms due to differences in calibration standards, antibody specificity and sample preparation requirements. This variability complicates obtaining cross-study comparisons and universal cut-off value definitions (43). The preferred sample type is serum, as plasma anticoagulants and residual fibrinogen may introduce assay interference by interfering with antibody binding (44). Even in serum samples, lipids, fibrin and inadequate centrifugation can introduce measurement error, while storage conditions differ between research and routine clinical laboratories. These factors contribute to variation between different laboratories that may exceed normal biological differences between patient groups (45,46). Analytical performance and laboratory requirements of the most widely used assays for PICP and PIIINP are listed in Table 3 (47-51). While ECLIA-based methods show

Table 3. Analytical performance and laboratory requirements of the most widely used assays for procollagen type I C-terminal propeptide (PICP) and procollagen type III N-terminal propeptide (PIIINP)

Assay*	Method	Sample Type	Detection limit	Intra-assay variability	Inter-assay variability	Remarks‡
Takara Bio PICP	Sandwich ELISA	Serum	~ 0.2 ng/mL	< 5%	< 7%	Manual ELISA; widely used in research, 96-well format
Orion Diagnostica UniQ PIIINP	Radioimmunoassay	Serum	~ 1 µg/L	~ 5%	~ 7%	Historical use; requires radiation license
General†	ECLIA	Serum	~ 0.1-0.5 ng/mL	< 3-5%	< 5-8%	Fully automated; high analytical precision; low sample volume; superior reproducibility
Cloud-Clone PICP	Competitive ELISA	Serum	~ 0.1 ng/mL	< 10%	< 12%	Research use only; limited clinical validation
MyBioSource PIIINP	Competitive ELISA	Serum	3.12 ng/ml	< 15%	< 15%	Research-grade; manual handling

*From (47–51). †Performance values reflect the general analytical characteristics of ECLIA as standardized platform technology. Specific commercial ECLIA assays for PICP and PIIINP are not yet widely available. Values shown are based on validated ECLIA platforms reported in (51). ‡No standardized reference intervals or clinically validated cut-off values are currently available for circulating PICP or PIIINP as thresholds for myocardial viability or revascularization decision-making; reported values in the literature are assay- and disease-specific. ELISA - enzyme-linked immunosorbent assay. ECLIA - electrochemiluminescence immunoassay.

higher precision, greater automation and lower analytical variability, they are poorly harmonized across different manufacturers and reference ranges have not been standardized (51). On the other hand, ELISA kits are widely employed in research settings, but their higher inter-batch variability and operator-dependency limit clinical translation (52). Therefore, assay choice may impact study outcomes as much as underlying biological variation limiting the interpretation of PICP and PIIINP (53).

Concentrations of PIIINP are positively correlated with diastolic dysfunction in patients with heart failure with reduced ejection fraction, as well as left ventricular mass index and relative wall thickness in patients with left ventricular hypertrophy who have undergone successful coarctation of the aorta repair (54,55). A cross-sectional study conducted by Yang *et al.* demonstrated that in patients with hypertrophic cardiomyopathy, plasma PICP concentrations correlated with myocardial PICP content and myocardial collagen volume fraction on histology (56). Ferreira *et al.* showed that PICP concentrations were significantly higher in hypertensive patients before treatment (57).

In the study by Raafs *et al.,* fibrosis was quantified in 209 patients with dilated cardiomyopathy using endomyocardial biopsy with determination of collagen volume fraction, CMR with late gadolinium enhancement and circulating PICP and PIIINP concentrations (58). They found that circulating PICP concentrations were significantly higher in patients with myocardial fibrosis on CMR (91 (67–112) ng/mL *vs.* 77 (62–97) ng/mL, P = 0.02). RNA sequencing of endomyocardial biopsy tissue confirmed the increased expression of pro-inflammatory and pro-fibrotic pathways in patients with elevated PICP concentrations, and also demonstrated significant correlation with histologically proven myocardial fibrosis (R^2 = 0.17, P = 0.001). Furthermore, PICP was independently associated with adverse cardiovascular events and mortality. They did not find such association or correlation with PIIINP (58).

In patients with non-ischemic dilated cardiomyopathy, elevated serum concentrations of PICP and PIIINP were associated with CMR findings of myocardial fibrosis (156 ng/mL *vs.* 74 ng/mL, P < 0.001; and 5.1 ng/mL *vs.* 3.5 ng/mL, P < 0.001, respectively). Additionally, a cut-off value of 44.4 ng/mL for PICP predicted myocardial fibrosis with 77.5% sensitivity, 76% specificity and a negative predictive value of 85.5%, while PIIINP at a cut-off value of 1.18 ng/mL had a 71.83% sensitivity, 83% specificity and a negative predictive value of 83.6% (59). However, these cut-off values were derived from a single disease and cannot be assumed for ischemic diseases or viability assessment due to different underlying mechanisms. No universally accepted diagnostic cut-offs exist for PICP or PIIINP; their values currently remain disease dependent and cannot be applied as criteria for revascularization.

The clinical diagnostic utility of PICP and PIIINP was investigated in a systematic review and meta-analysis conducted by Zhang *et al.* (60). They reviewed 1130 records from four databases and included 12 studies after independent screening. The results confirmed that patients with myocardial fibrosis had significantly elevated serum PICP (95% confidence interval (CI) = 0.40 to 1.40) and PIIINP (95% CI = 0.04 to 1.23) (60). A study by Ravassa *et al.* explored utility of PICP in differentiating patients with heart failure who would be more likely to experience myocardial recovery. They found that patients with lower PICP (< 108.1 ng/mL) showed greater left ventricular reverse remodelling and lower risk of outcome related to heart failure (61).

Patient characteristics such as age, body mass index, comorbidities and heart failure treatment (particularly spironolactone) can alter concentrations of these biomarkers by their effect on collagen turnover (62). It has been suggested that propeptides may be incorporated in the collagen fibre network, preventing them from being cleaved leading to underestimation of true PICP and PIIINP concentrations even in patients with extensive myocardial fibrosis (63). Also, circulating concentrations reflect systemic fibrosis; elevated concentrations may originate from non-cardiac fibrosis involving the liver, kidneys, bones or lungs. Therefore, increased concentration does not necessarily reflect *in situ* myocardial fibrosis (40). This popula-

tion-dependent variability and lack of tissue specificity negatively impact the ability of PICP and PIINP to discriminate reversible from irreversible myocardial dysfunction which is required to guide revascularization decisions.

Galectin-3

Galectin-3 regulates several cellular functions: growth, differentiation, proliferation, adhesion, apoptosis and tissue repair (64). Most commonly, it is located in the cytoplasm, as well as being expressed on the cellular surface. It is then secreted into biological fluids such as urine and blood. Additionally, injured and inflammatory cells release it under different pathological conditions (18). Galectin-3 is a potent inflammatory protein involved in acute and chronic inflammation by initiating and amplifying the inflammatory response (65,66).

It is measured in plasma or serum using immunoassay-based techniques, most commonly ELISA or ECLIA (67). Galectin-3 concentrations do not differ significantly when measured in serum or plasma (68). Commercially available assays have different sensitivity and specificity, with reported limits of detection typically ranging from 0.1-0.3 ng/mL. Intra- and inter-assay coefficients of variation of different platforms are typically under 10% which is acceptable for clinical use, although platform-specific variability remains a major limitation to clinical interpretation (69). Consequently, Gal-3 concentrations cannot be directly compared across studies unless the same assay platform is used, while the absence of cross-platform standardization prevents establishment of universal cut-off values. Therefore, reported Gal-3 normal ranges cannot be uniformly applied and assay-specific interpretation remains necessary.

A study on rat models after myocardial infarction showed increased concentrations of Gal-3 and a later peak in non-infarcted myocardium demonstrating its role in cardiac remodelling (70). In a study by Liu *et al*., they infused Gal-3 into rats intrapericardially and reported its overexpression compromising the cardiomyocyte´s viability. They also noted elevated mast cell and macrophage infiltration, increased perivascular and interstitial fibrosis and cardiac hypertrophy (71).

Expression of Gal-3 is associated with increased fibroblast activity, ECM accumulation and production of collagen in the myocardium. It is also expressed in fibroblasts and macrophages after stressful events (72,73). After activation, it forms a complex with transforming growth factor beta on the cell surface which stimulates fibrosis development. This signal, along with mechanical stress, transforms fibroblasts into active myofibroblasts that produce collagen (74).

Some recent studies investigated the Gal-3 upper reference limit in a healthy population of blood donors. They measured Gal-3 by using the Architect STAT Galectin-3 immunoassay. Median Gal-3 plasma concentration was 14.3 ng/mL (interquartile range 11.9-16.7 ng/mL), while the 97.5th percentile upper reference limit (URL) of normal in their study population (90% CI) was 26.1 (23.3-31.5) ng/mL. No sex-related differences were found. In contrast, age was a confounding variable that affected its concentration – the URL of Gal-3 was found to be higher in older (> 45 years) than in younger subjects (31.5 (26.2-51.4) *vs*. 21.8 (21-26.1) ng/mL, respectively) (75,76). This indicates that population-based reference intervals are affected by age, as well as being assay-specific, limiting their routine clinical interpretation.

In a study of patients with non-ischemic dilated cardiomyopathy, elevated Gal-3 concentrations were associated with findings of myocardial fibrosis on CMR (17.7 ng/mL *vs*. 9.1 ng/mL, $P < 0.001$). Furthermore, a cut-off value of 11 ng/mL predicted myocardial fibrosis with 90.4% sensitivity, 66.1% specificity and 92% negative predictive value (59). These thresholds were derived from a single disease entity, which cannot be anticipated for viability assessment in ischemic disease due to different underlying mechanisms. For example, remodelling after myocardial infarction involves acute macrophage activation and transient sharp Gal-3 elevation, while chronic ischemic disease is characterized by lower inflammatory markers as part of chronic interstitial fibrosis. Consequently, similar Gal-3 concentrations may reflect transient and reversible inflammation in certain patients but irreversible fibrosis in others, depending on the remodelling mechanism (64,77).

Galectin-3 measurement is endorsed by the 2017 Guidelines of the American Heart Association for assessing risk and evaluating prognosis of patients with heart failure. Different mechanisms are involved in the promotion of heart failure by Gal-3, some of which are: inflammatory cell infiltration, fibroblast proliferation and cardiomyocytes hypertrophy (64). The threshold of 17.8 ng/mL is often considered to successfully discriminate between low-risk and high-risk for clinical complications in heart failure patients (74).

Galectin-3 has also been investigated in other cardiovascular diseases, especially those initiated and stimulated by inflammation, where elevated concentrations reflect disease activity and severity, as well as adverse prognosis (78-82). In a study by Screever *et al.* they investigated the association of CMR-identified fibrosis with Gal-3 after myocardial infarction. Concentrations of Gal-3 were higher in patients with CMR-identified fibrosis (20 *vs.* 15 ng/mL, P = 0.004) (83). In another study by Asleh *et al*., Gal-3 concentrations above 15.1 ng/mL were associated with a higher risk of heart failure and death after myocardial infarction, even after adjustment for age, sex, comorbidities and troponin levels (84). A study by Sherpa *et al.* showed that elevated concentrations of Gal-3 are associated with a higher risk of myocardial fibrosis and sudden cardiac death (85). This shows the importance of larger studies that would target Gal-3 to prevent myocardial fibrosis and lower the risk of sudden cardiac death.

Limitations and clinical utility of fibrosis biomarkers in predicting myocardial viability

Even though circulating biomarkers such as PICP, PIIINP and Gal-3 reflect remodelling of the ECM, they have rarely been studied in association with functional recovery after revascularization, the clinical definition of myocardial viability. Published data mostly investigate their correlation with fibrosis burden on non-invasive imaging, without an evaluation of contractility improvement, perfusion or symptom relief after revascularization (43,63). Additionally, elevated circulating biomarker concentrations do not indicate irreversible scar, as they may also reflect active inflammation or diffuse interstitial fibrosis without loss of function (64). Different concentrations across various cardiovascular diseases, limited tissue specificity and lack of standardized cut-offs reduce their discriminative power in distinguishing reversible from irreversible myocardial dysfunction. There is currently no biomarker cut-off that reliably differentiates myocardium capable of recovery from an irreversible scar.

They provide information on underlying biological processes of myocardial remodelling, but currently lack outcome-based validation. Consequently, their use remains primarily experimental. They should be interpreted as complementary indicators of remodelling, not as the determinants of revascularization decisions. Well-designed clinical studies incorporating biomarkers with contemporary imaging are required before their usage in routine viability assessment.

To enable comparison of the available circulating fibrosis biomarkers, Table 4 summarizes their underlying biological pathways, commonly used analytical methods, current level of clinical validation and key strengths and limitations.

Telomere length determination as an emerging biomarker of myocardial fibrosis

Cellular aging and repeated inflammatory or oxidative stress progressively shorten the telomeres. These processes are also integral to fibroblast activation and ECM expansion (86). Studies have shown that shortened leukocyte telomeres correlate with the degree of cardiac aging (87).

Telomere length can be measured with fluorescence in-situ hybridization (flow-FISH), quantitative polymerase chain reaction (PCR) or Southern blot analysis, with quantitative PCR being the most widely used because of its low sample requirements and scalability. Nevertheless, lack of standardized reference ranges, assay variability and low specificity currently limit its clinical application (88).

Despite these limitations, telomere length assessment provides insight into the burden of remodelling and cellular stress. In future, it may complement other biomarkers to improve stratification of

Table 4. Comparison of circulating fibrosis biomarkers relevant to myocardial viability assessment

Biomarker	Biological pathway	Analytical methods	Clinical validation	Strengths	Limitations
PICP	Collagen type I synthesis Replacement and interstitial fibrosis	ELISA RIA ECLIA	Moderate Correlates with CMR fibrosis, biopsy collagen volume fraction, remodelling and outcomes in heart failure Limited data in ischemic viability	Strongest correlation with collagen type I turnover Automated ECLIA platforms available Independent association with adverse outcomes	Affected by systemic fibrosis (bone, liver) Assay variability and lack of harmonized cut-offs Underestimates fibrosis if propeptides remain in extracellular matrix
PIIINP	Collagen type III synthesis Early interstitial fibrosis	ELISA RIA ECLIA	Low–moderate Associated with heart failure severity and remodelling	Reflects dynamic collagen turnover Useful in heart failure and hypertrophic cardiomyopathy	Less specific for myocardial fibrosis Higher biological variability Influenced by liver disease, obesity, systemic inflammation Limited prognostic value
Galectin-3	Macrophage activation Inflammation Fibrosis signalling Fibroblast proliferation	ELISA ECLIA	Moderate Validated predictor of heart failure hospitalization and mortality Correlates with diffuse fibrosis on CMR	Reflects upstream fibrotic signalling Stable in serum/plasma Large body of clinical outcome data	Not specific to cardiac tissue Influenced by age and renal function Assay variability and non-unified reference intervals Elevations may reflect inflammation

PICP - procollagen type I C-terminal propeptide. PIIINP - procollagen type III N-terminal propeptide. ELISA - enzyme-linked immunosorbent assay. RIA - radioimmunoassay. ECLIA - electrochemiluminescence immunoassay. CMR - cardiac magnetic resonance.

patients with chronic coronary syndrome, especially those with CTO in whom the degree of irreversible remodelling influences viability and benefit from revascularization.

Conclusion

Reliable myocardial viability evaluation represents a key step in selecting patients with chronic coronary syndrome and CTO who are most likely to benefit from revascularization. Circulating fibrosis biomarkers, such as PICP, PIIINP and Gal-3 reflect ECM remodelling and may complement non-invasive imaging modalities in identifying patients with irreversible myocardial fibrosis who are less likely to benefit from revascularization. However, these biomarkers are currently associated with fibrosis burden rather than functional recovery after revascularization. No biomarker cut-off has been prospectively validated in large-scale studies to reliably discriminate reversible dysfunction from irreversible scar.

Circulating fibrosis biomarkers should therefore be used as adjunctive tools that reflect underlying biological processes, not as standalone guides for revascularization decisions. Their integration into clinical guidelines and pathways requires large-scale prospective outcome-based studies that link biomarker concentrations with contractility recovery and perfusion improvement. Future research should focus on standardizing assays and reference intervals, finding disease-specific cut-offs that differentiate acute inflammation from established fibrosis, as well as prospective strategies that combine biomarkers with advanced non-invasive imaging modalities.

Author contributions

Ž Dragila Tomašić: Conceptualization, Methodology, Supervision, Writing – original draft, Writing –

review & editing; A Mikolčić: Visualisation, Writing – review & editing; L Maršić: Visualisation, Writing – review & editing; L Maričić: Visualisation, Writing – review & editing; K Selthofer Relatić: Supervision, Writing – review & editing; D Šnajder Mujkić: Conceptualization, Supervision, Writing – review & editing

Potential conflict of interest

None declared.

Data availability statement

No data was generated during this study, so data sharing statement is not applicable to this article.

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