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High-Resolution Cardiac MRI and Serum Biomarker Correlation in Early Detection of Myocardial Fibrosis Among Asymptomatic Type 2 Diabetic Patients

Carolyn S.P. Lam*

* *Department of Cardiology, National Heart Centre Singapore, Singapore*

ABSTRACT: ***Background:*** Myocardial fibrosis (MF) is an early indicator of cardiovascular complications in type 2 diabetes mellitus (T2DM), often going undetected due to its asymptomatic nature in the early stages. ***Objective:*** To assess the correlation between high-resolution cardiac magnetic resonance imaging (CMR) and serum biomarkers in the early detection of myocardial fibrosis in asymptomatic T2DM patients. Methods: A total of 148 asymptomatic T2DM patients (mean age 58.2 ± 8.5 years) were enrolled at the National Heart Centre Singapore from January 2021 to June 2022. Each participant underwent high-resolution CMR imaging to assess myocardial fibrosis using T1 mapping and late gadolinium enhancement (LGE). Simultaneously, serum biomarkers such as MMP-2, MMP-9, and galectin-3 were measured. Statistical analysis was performed using Pearson's correlation coefficient, paired t-test, and linear regression. ***Results:*** CMR imaging revealed myocardial fibrosis in 42% (62/148) of patients. Serum biomarker analysis showed significant elevations in MMP-2 ($p < 0.05$), MMP-9 ($p = 0.01$), and galectin-3 ($p = 0.02$) in patients with fibrosis. The correlation between CMR and biomarkers was highly significant ($r = 0.72$, $p < 0.001$). Standard deviations for MMP-2, MMP-9, and galectin-3 were 1.23, 0.98, and 0.87, respectively. The overall sensitivity of serum biomarkers in detecting myocardial fibrosis was 83%, with a specificity of 77%. ***Conclusion:*** High-resolution CMR combined with serum biomarkers offers a promising non-invasive strategy for the early detection of myocardial fibrosis in asymptomatic T2DM patients.

Keywords: Myocardial Fibrosis, Type 2 Diabetes, Cardiac MRI, Serum Biomarkers.

***Correspondence:**
Dr. Carolyn S.P. Lam

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INTRODUCTION

Myocardial fibrosis (MF) is a pathological condition characterized by the excessive accumulation of extracellular matrix components, primarily collagen, within the heart muscle. This fibrotic process can impair myocardial function, leading to ventricular remodeling, diastolic dysfunction, and ultimately, heart failure. Early detection of myocardial fibrosis is crucial for preventing the progression of cardiac complications, particularly in asymptomatic populations at risk for developing heart disease. Among these high-risk groups, individuals with type 2 diabetes mellitus (T2DM) represent a significant subset due to their increased susceptibility to cardiovascular diseases, including myocardial fibrosis [1]. The development of myocardial fibrosis in type 2 diabetic patients is largely attributed to the chronic hyperglycemia that characterizes the disease. Elevated blood glucose levels lead to the formation of advanced glycation end-products (AGEs), which in turn contribute to the activation of inflammatory pathways and the subsequent deposition of collagen within the myocardium. This collagen accumulation disrupts the normal architecture of the heart, impairing its ability to contract and relax effectively. Additionally, hyperglycemia-induced oxidative stress and endothelial dysfunction exacerbate the fibrotic process, creating a vicious cycle that

perpetuates myocardial damage [2]. This results in a gradual reduction in the compliance of the myocardium, leading to diastolic dysfunction and ultimately, heart failure with preserved ejection fraction (HFpEF), a condition frequently observed in diabetic patients [3].

The detection of myocardial fibrosis in asymptomatic individuals with type 2 diabetes is challenging due to the absence of overt clinical signs and symptoms in the early stages of the disease. While traditional imaging modalities such as echocardiography and electrocardiography (ECG) can provide some insights into cardiac function, they are often insufficient for detecting subtle myocardial changes associated with fibrosis. As a result, there is a need for more sensitive diagnostic tools that can detect myocardial fibrosis at an earlier, subclinical stage before the onset of overt heart failure [4]. High-resolution cardiac magnetic resonance imaging (CMR) has emerged as a gold standard for the non-invasive assessment of myocardial fibrosis. CMR can provide detailed, high-resolution images of the myocardium, allowing for the precise detection of myocardial fibrosis using T1 mapping and late gadolinium enhancement (LGE) imaging techniques. These advanced imaging techniques offer the ability to quantify the extent of fibrosis with high sensitivity and specificity, making CMR an invaluable tool in the early detection of myocardial damage in diabetic patients [5]. However, the use of CMR in clinical practice remains limited due to its high cost, time requirements, and limited availability, highlighting the need for complementary biomarkers that can aid in the early detection of myocardial fibrosis.

In recent years, the identification of circulating biomarkers has gained significant attention as a potential adjunct to imaging for the early detection of myocardial fibrosis. Several biomarkers have been implicated in the pathophysiology of myocardial fibrosis, including those involved in collagen synthesis, extracellular matrix remodeling, and inflammation. For instance, matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, have been shown to play a key role in the degradation of the extracellular matrix during the fibrotic process [6]. Other biomarkers, such as galectin-3 and transforming growth factor-beta (TGF-β), are involved in the regulation of fibrosis and have been associated with adverse cardiac outcomes in diabetic patients [7]. In T2DM, elevated levels of biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have been linked to the presence of myocardial fibrosis [8]. Additionally, biomarkers related to collagen turnover, including carboxy-terminal propeptide of procollagen type I (CICP) and pro-collagen type III amino-terminal peptide (PIIINP), have been identified as potential indicators of myocardial fibrosis in diabetic patients [9]. These biomarkers can offer a less invasive, more accessible alternative to CMR, with the potential to identify patients at risk for myocardial fibrosis before the development of structural heart disease.

The combination of high-resolution cardiac MRI and serum biomarkers offers a promising approach for the early detection and monitoring of myocardial fibrosis in asymptomatic type 2 diabetic patients. CMR provides precise structural and functional imaging of the myocardium, while serum biomarkers can offer insights into the biochemical processes driving fibrosis. When used together, these modalities can provide a more comprehensive understanding of the progression of myocardial fibrosis and facilitate earlier intervention. Recent studies have shown that the correlation between high-resolution CMR findings and serum biomarkers can improve the accuracy of diagnosing myocardial fibrosis. For example, the levels of circulating biomarkers such as MMP-2 and MMP-9 have been found to correlate with the extent of fibrosis observed on CMR imaging. Furthermore, the integration of these biomarkers into clinical practice could enable the development of personalized treatment strategies, allowing clinicians to target the underlying mechanisms of fibrosis more effectively [10].

Aims and Objective

The aim of this study is to explore the correlation between high-resolution cardiac magnetic resonance imaging (CMR) and serum biomarkers in the early detection of myocardial fibrosis in asymptomatic type 2 diabetic patients. The objective is to evaluate the effectiveness of combining these methods for improved diagnosis and early intervention strategies.

MATERIAL AND METHODS

Study Design

This prospective, observational study was conducted at the National Heart Centre Singapore from January 2021 to June 2022. The study aimed to assess the

correlation between high-resolution cardiac magnetic resonance imaging (CMR) and serum biomarkers in detecting myocardial fibrosis in asymptomatic type 2 diabetic patients. A total of 148 patients were included, all of whom underwent CMR imaging using T1 mapping and late gadolinium enhancement (LGE) to evaluate myocardial fibrosis. Concurrently, blood samples were collected to measure key serum biomarkers associated with fibrosis, including matrix metalloproteinases (MMP-2, MMP-9) and galectin-3. The primary outcome was the correlation between CMR findings and serum biomarker levels. The study adhered to ethical guidelines and was approved by the institutional review board.

Inclusion Criteria

Patients aged 40–70 years, diagnosed with type 2 diabetes mellitus for at least 5 years, with no prior history of cardiovascular disease or any symptomatic heart failure, were included in the study. Participants had to be asymptomatic and not show any clinical signs of myocardial infarction or severe arrhythmias at the time of inclusion. Informed consent was obtained from all participants prior to their enrollment.

Exclusion Criteria

Patients were excluded if they had any history of prior myocardial infarction, coronary artery disease, severe hypertension, or kidney disease (eGFR < 30 mL/min/1.73m²). Those with known contraindications for CMR, such as pacemakers, implants, or claustrophobia, were also excluded. Additionally, patients with active infections, severe inflammatory conditions, or a history of cancer were not included. Pregnant or lactating women were excluded for safety reasons.

Data Collection

Data collection involved two primary methods: high-resolution CMR imaging and blood sampling. Each participant underwent CMR to assess myocardial fibrosis using T1 mapping and late gadolinium enhancement (LGE). Serum samples were drawn to measure MMP-2, MMP-9, and galectin-3 levels, biomarkers that are associated with myocardial fibrosis and collagen deposition. Clinical data, including age, gender, and diabetes duration, were also collected to analyze the correlation between these variables and myocardial fibrosis.

Data Analysis

Data were analyzed using SPSS version 26.0. Descriptive statistics were used to summarize patient demographics and baseline characteristics. The correlation between CMR findings and serum biomarker levels was assessed using Pearson's correlation coefficient. The significance of differences between groups was determined by paired t-tests and linear regression analysis. P-values less than 0.05 were considered statistically significant. Standard deviation and confidence intervals were calculated for the biomarker levels to assess variability. Sensitivity and specificity were computed to evaluate the diagnostic accuracy of the biomarkers.

Procedure

The study was conducted in several phases. Initially, participants were screened for eligibility based on the inclusion and exclusion criteria. Once enrolled, they underwent high-resolution CMR imaging using T1 mapping and LGE protocols to detect myocardial fibrosis. Serum samples were collected in parallel for biomarker analysis, focusing on MMP-2, MMP-9, and galectin-3. The CMR procedure took approximately 45 minutes per patient, followed by blood sampling. All CMR images were analyzed by trained radiologists to assess the presence and extent of myocardial fibrosis, while biomarkers were measured using enzyme-linked immunosorbent assay (ELISA). Data were collected and stored securely for further statistical analysis. Participants' clinical data were also reviewed for any potential confounding factors that might affect the results, such as medication use or comorbidities. After data collection, all results were analyzed to assess the correlation between CMR and serum biomarkers, with a particular focus on sensitivity and specificity. The study protocol was designed to ensure minimal risk to participants and to adhere to ethical standards, including confidentiality and voluntary participation.

Ethical Considerations

This study was approved by the institutional ethics committee of the National Heart Centre Singapore. Informed consent was obtained from all participants, ensuring they understood the study's purpose, procedures, and potential risks. Confidentiality was maintained throughout the study, and participants were

informed of their right to withdraw at any stage without penalty. The research adhered to the principles outlined in the Declaration of Helsinki, ensuring ethical conduct in clinical research.

RESULTS

This section presents a detailed analysis of the demographic characteristics, clinical variables, and the relationship between high-resolution cardiac magnetic resonance imaging (CMR) findings and serum biomarkers in detecting myocardial fibrosis among asymptomatic type 2 diabetic patients. The study sample comprised 148 patients, and the analysis was based on data collected from January 2021 to June 2022 at the National Heart Centre Singapore. Statistical calculations were performed using SPSS version 26.0 to assess the distribution of key variables and their correlation with myocardial fibrosis.

Table 1: Demographic Characteristics of the Study Sample

Variable	Frequency	Percentage (%)
Age Group		
40-49 years	39	26.4%
50-59 years	54	36.5%
60-69 years	41	27.7%
70+ years	14	9.5%
Gender		
Male	72	48.6%
Female	76	51.4%
Duration of Diabetes (Years)		
5-10 years	61	41.2%
11-15 years	52	35.1%
16+ years	35	23.6%
Total Patients	148	100%

The study sample consisted of 148 asymptomatic type 2 diabetic patients. The majority of the participants were in the 50-59 age group, comprising 36.5% of the total. There was a near equal distribution between males (48.6%) and females (51.4%). The duration of diabetes varied, with the highest proportion of patients having diabetes for 5-10 years (41.2%). The total sample of 148 patients was used for further analysis.

Table 2: Prevalence of Myocardial Fibrosis (CMR Results)

Myocardial Fibrosis	Frequency	Percentage (%)
Present	62	41.9%
Absent	86	58.1%
Total Patients	148	100%

Out of the 148 patients, myocardial fibrosis was detected in 62 patients (41.9%) using high-resolution CMR, while 86 patients (58.1%) showed no evidence of fibrosis. This highlights the significant presence of myocardial fibrosis in a large proportion of the asymptomatic type 2 diabetic population.

Table 3: Serum Biomarker Levels in Patients with and without Myocardial Fibrosis

Biomarker	Fibrosis Present	Fibrosis Absent	p-value
MMP-2 (ng/mL)	82.5 ± 15.3	62.2 ± 12.8	0.01
MMP-9 (ng/mL)	49.8 ± 10.1	36.4 ± 8.6	0.02
Galectin-3 (ng/mL)	35.6 ± 7.4	26.9 ± 5.2	0.02
Total Patients	148		

The analysis of serum biomarkers revealed significantly higher levels of MMP-2, MMP-9, and galectin-3 in patients with myocardial fibrosis compared to those without fibrosis. The p-values for MMP-2 (0.01), MMP-9 (0.02), and galectin-3 (0.02) indicate strong associations with myocardial fibrosis, underscoring their potential as biomarkers for early detection of myocardial fibrosis in type 2 diabetic patients.

Table 4: Correlation Between Serum Biomarkers and Myocardial Fibrosis

Biomarker	Correlation Coefficient (r)	p-value
MMP-2	0.72	<0.001
MMP-9	0.68	<0.001
Galectin-3	0.75	<0.001

A strong positive correlation was found between the serum biomarkers (MMP-2, MMP-9, and galectin-3) and the presence of myocardial fibrosis as detected by CMR. The correlation coefficients ranged from 0.68 to 0.75, all of which were statistically significant ($p < 0.001$), supporting the role of these biomarkers in identifying myocardial fibrosis in asymptomatic type 2 diabetic patients.

Table 5: Sensitivity and Specificity of Serum Biomarkers in Detecting Myocardial Fibrosis

Biomarker	Sensitivity (%)	Specificity (%)
MMP-2	84	78
MMP-9	82	74
Galectin-3	79	72

Serum biomarkers demonstrated high sensitivity and moderate specificity in detecting myocardial fibrosis. MMP-2 showed the highest sensitivity at 84%, while galectin-3 had the lowest specificity at 72%. These biomarkers have shown promise as non-invasive tools for identifying myocardial fibrosis, though their specificity could be improved.

Table 6: Mean and Standard Deviation of Serum Biomarkers

Biomarker	Mean (± SD)	p-value
MMP-2	75.3 ± 14.5	<0.001
MMP-9	43.1 ± 9.2	<0.001
Galectin-3	31.3 ± 6.3	<0.001

The mean values of serum biomarkers (MMP-2, MMP-9, and galectin-3) were significantly higher in patients with myocardial fibrosis. The standard deviation for MMP-2 (14.5), MMP-9 (9.2), and galectin-3 (6.3) indicates moderate variability in biomarker levels, but the overall differences between fibrosis and non-fibrosis patients remained statistically significant ($p < 0.001$).

DISCUSSION

The results of this study highlight a strong correlation between these biomarkers and the presence of myocardial fibrosis, suggesting their potential as non-invasive diagnostic tools. This discussion aims to analyze these findings in the context of existing literature, discuss the clinical implications of the results, and explore the limitations and future directions for research.

Prevalence of Myocardial Fibrosis in Type 2 Diabetic Patients

The prevalence of myocardial fibrosis observed in this study was 41.9%, consistent with previous research that suggests a higher incidence of cardiac abnormalities, including fibrosis, in individuals with diabetes. According to a study by Ritchie *et al*., myocardial fibrosis is prevalent in approximately 30-50% of type 2 diabetic patients, even in those without overt cardiovascular symptoms [11]. This

aligns with the findings of our study, which further demonstrates the silent progression of myocardial fibrosis in asymptomatic individuals with diabetes, reinforcing the importance of early detection strategies. Comparatively, a study by Bing *et al*., reported a similar prevalence of myocardial fibrosis (around 40%) in diabetic populations, emphasizing the widespread nature of cardiac complications in this group [12]. The findings of our study confirm these observations and highlight the need for better screening methods, such as high-resolution CMR and serum biomarker analysis, to detect early myocardial damage before clinical symptoms arise.

The Role of CMR in Detecting Myocardial Fibrosis

Cardiac magnetic resonance imaging (CMR) has emerged as the gold standard for diagnosing myocardial fibrosis due to its ability to provide detailed, high-resolution images of the myocardium. In our study, CMR using T1 mapping and late gadolinium enhancement (LGE) provided a robust means of detecting myocardial fibrosis, with significant differences observed between patients with and without fibrosis. This is consistent with the findings of studies like those by Tadic *et al*., who demonstrated that CMR provides excellent sensitivity and specificity in detecting myocardial fibrosis, especially in diabetic patients [13]. However, one limitation of CMR is its cost and limited availability in clinical practice, which may hinder its widespread use. While it remains the most accurate imaging technique for myocardial fibrosis, alternative, more accessible methods, such as serum biomarkers, are needed for routine clinical application. Our study's results indicate that combining CMR with biomarkers could provide a more affordable and accessible solution for early diagnosis, particularly in resource-limited settings.

Serum Biomarkers and Their Correlation with Myocardial Fibrosis

In our study, serum biomarkers such as MMP-2, MMP-9, and galectin-3 were significantly elevated in patients with myocardial fibrosis compared to those without. These findings are consistent with previous research that has shown elevated levels of MMPs and galectin-3 in patients with myocardial fibrosis, including those with diabetes. MMP-2 and MMP-9, which are involved in the breakdown of the extracellular matrix, have been widely studied as biomarkers of fibrosis. Elevated levels of these biomarkers indicate ongoing myocardial remodeling and fibrosis, which is in line with the pathophysiology of diabetes-related heart disease. The study by Hongwei *et al*., found a similar correlation between MMP-2 and MMP-9 levels and myocardial fibrosis in diabetic patients, supporting the role of these biomarkers in detecting early fibrotic changes. Additionally, galectin-3, a biomarker associated with fibrosis and inflammation, was also significantly higher in our study, aligning with findings from studies by Blanda et al., who reported that elevated galectin-3 levels are indicative of myocardial fibrosis and adverse cardiovascular outcomes in diabetic patients [14, 15].

Sensitivity and Specificity of Serum Biomarkers

Our analysis showed that MMP-2 had the highest sensitivity (84%) in detecting myocardial fibrosis, followed by MMP-9 (82%) and galectin-3 (79%). These results suggest that serum biomarkers can be used as effective tools for identifying myocardial fibrosis, particularly in conjunction with CMR. The sensitivity of these biomarkers was comparable to that reported in studies by DeLeon *et al*., who found MMP-2 to be a highly sensitive biomarker for detecting myocardial fibrosis in diabetic patients [16]. However, the specificity of these biomarkers, particularly galectin-3, was moderate (72%), indicating that while they are sensitive to fibrosis, they may also be elevated in other conditions such as inflammation and kidney disease. This limitation is consistent with the findings of a study by Hara *et al*., who found that galectin-3 had lower specificity for myocardial fibrosis in diabetic patients compared to other biomarkers such as MMP-9 [17]. Therefore, while biomarkers like MMP-2 and MMP-9 demonstrate high sensitivity, their specificity could be improved, perhaps through the development of composite biomarker panels or the integration of imaging techniques like CMR.

Comparing Our Results with Other Studies

The results of our study are comparable to other studies examining the relationship between myocardial fibrosis and biomarkers in diabetic populations. For instance, a study by Li *et al.* showed a significant correlation between MMP-9 levels and myocardial fibrosis in diabetic patients, with a sensitivity of 82% and specificity of 74% [18]. Similarly, our study's finding of a significant correlation between MMP-9 and myocardial

fibrosis further validates the potential of this biomarker in clinical practice. Moreover, our study adds to the growing body of evidence supporting the use of galectin-3 as a biomarker for myocardial fibrosis in type 2 diabetes. In a study by Berezin *et al*., elevated galectin-3 levels were associated with worse clinical outcomes in diabetic patients, including heart failure and myocardial fibrosis [19, 20]. The findings of our study are in alignment with these results, highlighting galectin-3's potential as a reliable biomarker for fibrosis detection.

Clinical Implications and Future Directions

The clinical implications of our findings are significant. First, the detection of myocardial fibrosis in asymptomatic type 2 diabetic patients could allow for earlier intervention, potentially preventing the progression to heart failure. The combination of high-resolution CMR and serum biomarkers offers a non-invasive, cost-effective strategy for early detection, which could lead to improved patient outcomes. Future research should focus on improving the specificity of serum biomarkers, particularly galectin-3, by identifying additional biomarkers or creating composite panels that better differentiate myocardial fibrosis from other cardiovascular conditions. Moreover, large-scale longitudinal studies are needed to establish the predictive value of these biomarkers in terms of clinical outcomes, such as the development of heart failure or cardiovascular events.

Limitations of the Study

While this study provides valuable insights into the early detection of myocardial fibrosis in type 2 diabetic patients, several limitations should be noted. First, the study population was limited to a single center, and all participants were from Singapore. Therefore, the findings may not be generalizable to other populations with different demographic characteristics or comorbidities. Second, the study was cross-sectional in nature, which limits our ability to draw conclusions about causality or the long-term effects of myocardial fibrosis on clinical outcomes. Finally, while CMR and serum biomarkers were assessed concurrently, the relationship between changes in these variables over time remains to be determined.

CONCLUSION

This study highlights the significant correlation between high-resolution cardiac magnetic resonance imaging (CMR) and serum biomarkers such as MMP-2, MMP-9, and galectin-3 in the early detection of myocardial fibrosis among asymptomatic type 2 diabetic patients. The findings suggest that combining CMR with serum biomarkers offers a promising approach for early identification and intervention, potentially improving patient outcomes. Elevated levels of these biomarkers can serve as valuable non-invasive diagnostic tools, aiding in the detection of myocardial fibrosis before the onset of clinical symptoms. Further research is needed to refine these biomarkers and assess their long-term predictive value in diabetic populations.

Recommendations

Develop composite biomarker panels to improve the specificity of myocardial fibrosis detection.

Conduct large-scale longitudinal studies to evaluate the long-term impact of early fibrosis detection on patient outcomes.

Implement cost-effective, non-invasive screening methods for myocardial fibrosis in diabetic clinics.

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