Threshold Concept of Carboxyterminal Telopeptide Type-I Collagen in Myocardial Interstitial Fibrosis and Left Ventricular Dilation among Patients with Atrial Fibrillation

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ABSTRACT

Impaired collagen turnover and risk factors such as hypertension, obesity, dyslipidemia and left ventricular dilation with wall thickness cause myocardial interstitial fibrosis and are all predisposing factors for atrial fibrillation disease. However, the most common symptoms of atrial fibrillation include palpitations, chest pain, dyspnea and syncope.

The study included 120 participants ranging in age from 22 to 90 years. Sixty of them had been diagnosed with fibrillation patients by electrocardiogram interpretation and the other sixty were healthy and used as a control group; the study was conducted at the Al-Zahraa Teaching Hospital in Al-Kut/Wasit/ Iraq. The serum carboxyterminal telopeptide type-I collagen level was measured by enzyme-linked immunosorbent assay, while the left ventricular diameter was evaluated by echocardiography.

Most atrial fibrillation patients with MIF have left ventricular dilation with thick walls and comorbidities such as obesity and hypertension. This study aimed to investigate the relationship between the level of carboxyterminal telopeptide type-I collagen and myocardial interstitial fibrosis in atrial fibrillation patients.

***Key Words**: Myocardial Interstitial Fibrosis, Atrial Fibrillation, Left Ventricular, Echocardiography and CITP*

الخلاصة.

يتسبب ضعف دوران الكولاجين وعوامل الخطر مثل ارتفاع ضغط الدم والسمنة وعسر شحميات الدم وتمدد البطين الأيسر مع سماكة الجدار في حدوث تليف الخلالي لعضلة القلب وجميعها عوامل تنبؤية لمرض الرجفان الأذيني. ومع ذلك، فإن الأعراض الأكثر شيوعًا للرجفان الأذيني تشمل الخفقان وألم الصدر وضيق التنفس والإغماء.

تضمنت الدراسة على 120 مشاركًا تتراوح أعمارهم بين ٢٢ -٩٠عامًا. تم تشخيص ستين منهم بمرضى الرجفان عن طريق تفسير مخطط كهربية القلب، بينما كان الستون الآخرون يتمتعون بصحة جيدة ويستخدمون كمجموعة تحكم؛ أجريت الدراسة في مستشفى الزهراء التعليمي في الكوت / واسط / العراق. تم قياس مستوى مصل CITP بواسة الاليزا، بينما تم تقييم قطر البطين الايسر بواسطة تخطيط صدى القلب.

معظم مرضى الرجفان الأذيني الذين يعانون من التليف الخلالي لعضلة القلب يمتلكون توسع البطين الايسرمع جدران سميكة وأمراض مصاحبة مثل السمنة وارتفاع ضغط الدم. هدفت هذه الدراسة إلى معرفة العلاقة بين مستوى CITP والتليف الخلالي لعضلة القلب لدى مرضى الرجفان الأذيني.

1-INTRODUCTION

Fibroblasts can be differentiated into myofibroblasts to control collagen turnover. Furthermore, mechanical stress released by hypertension, obesity, and dyslipidemia alter the function of fibroblasts and myofibroblasts, leading to myocardial interstitial fibrosis (MIF), left ventricular (LV) dilation with wall thickness and ejection fraction percentage (EF%) dysfunction [1, 2].

Cardiac fabric fibrosis as well as changes in cell architecture, cardiomyocyte dilatation [3], and interstitial fibrosis is considered hypertrophy and thickening of the extracellular matrix (ECM) [4]. Myofibroblast activation and cardiac myofibroblast secretion collagen in ECM representing 85% of procollagen type-1 ([5, 6]. Procollagen type-I in ECM converts into collagen propeptide by proteinase then collagen propeptide releasing into circulation and big collagen fibres convert telopeptides (CITP) by collagenase (Central illustration) then CITP is released into circulation [7, 8]. Myocardial collagen deposition and fibrosis have been associated with degradation biomarker (CITP) [9]. The MIF is crucial to myocardial remodelling in patients with heart failure (HF) caused by various non-ischemic diseases; It significantly impacts LV, EF% dysfunction and poor clinical results in non-ischemic heart disease [10]. AF is a heart arrhythmia characterised by the irregular and uncontrolled electrical activity of the atrium, which interferes with the contraction characteristics of the ventricular system thereby reducing cardiac function and leading to pain. A more common irregular heartbeat is associated with comorbidities and an increased mortality risk [11, 12]. Patients with atrial fibrillation have a 45-fold elevated probability of stroke a 23-fold increased risk of HF and a 2-fold increased risk of total death [13]. In addition, irregular RR intervals and the absence of conspicuous P waves on the electrocardiogram (ECG) distinguish AF rhythm [14, 15]. The following categorisation method is recommended for the management of AF as per the recommendations of the ACC, AHA and ESC [16, 17]:

Paroxysmal AF: Episodes that begin and finish spontaneously, typically lasting less than 24 hours but sometimes less than 7 days.

Persistent AF refers to episodes that last more than seven days but less than a year and necessitate pharmaceutical or electrical treatment to stop. Permanent AF refers to episodes that have endured for an extended period (more than a year) and have resisted all attempts to stop them.

Lone AF: Affects individuals smaller than 60 years old without clinical or echocardiographic causes.

The symptoms of AF vary a lot from person to person and even over time in the same person. However, the most prevalent symptoms include palpitations, chest pain, dyspnea and syncope [18, 19]. Not all reported symptoms are related to atrial fibrillation due to risk factors and comorbidities of AF that may create similar symptoms [18]. Asymptomatic AF has the same prognostic impact as symptomatic AF [20, 21]. Several risk factors have been identified as contributors to the onset and development of atrial fibrillation (AF) including non-modifiable risk factors such as age and gender and modifiable risk factors such as obesity, hypertension and dyslipidemia [22, 23, 24]. Additionally, these variables LV dilation [25, 26, 27].

2- PATIENTS AND METHODS

A case-control study included 120 participants divided into two groups: 60 healthy and 60 patients with atrial fibrillation who were present at the Cardiac Care Unit (CCU), cardiac consultations and emergency department at Al-Zahraa Teaching Hospital in Al-Kut/Wasit. The study inclusion criteria for participants were patients with non-ischemic atrial fibrillation, presence of comorbidities and absence of ischemic heart patients.

2.1. THE ETHICAL APPROVAL

The ethics committee of Kerbala University College of Medicine approved the study protocol. In addition, the study was conducted after review and written approval by the administrative and scientific association of Al-Zahraa Teaching Hospital/Wasit in Al-Kut City.

2.2. MEASURES

The study questionnaire included five tools measurement instruments: The ECG interpretation for diagnosis of atrial fibrillation, The echocardiography study for evaluating LV diameter, The ELISA Test for CITP level analysis, Abbot laboratories for lipid profiles test, monitoring for blood pressure measurement and a set of questions on demographic and clinical characteristics.

ECG interpretation can reveal cases of AF such as heartbeat (tachycardia), irregular, rapid and absence of p-wave.

The echocardiography study evaluates LV diameter dilation. LV dilation is a measurement of diameter as regards the interpretation of the LV diameter dilation and can be classified according to a report from the American College of Cardiology (ACC) [28]: (3.9-5.3 *cm* is within normal range, 5.4-5.7 *cm* suggest mild dilated, 5.8-6.1 *cm* refers to moderate dilated while more than 6.2 *cm* relates to severe dilated in females); (4.2-5.9 *cm* is within normal range, 6.0-6.3 *cm* suggest mild dilated, 6.4-6.8 *cm* refers to moderate dilated while more than 6.9 *cm* relates to severe dilated in the males). The Echocardiography study is a gold standard tool for recording cardiac severity changes.

The ELISA test for CITP analysis assesses myocardial interstitial fibrosis intensity in ventricular fibrosis patients.

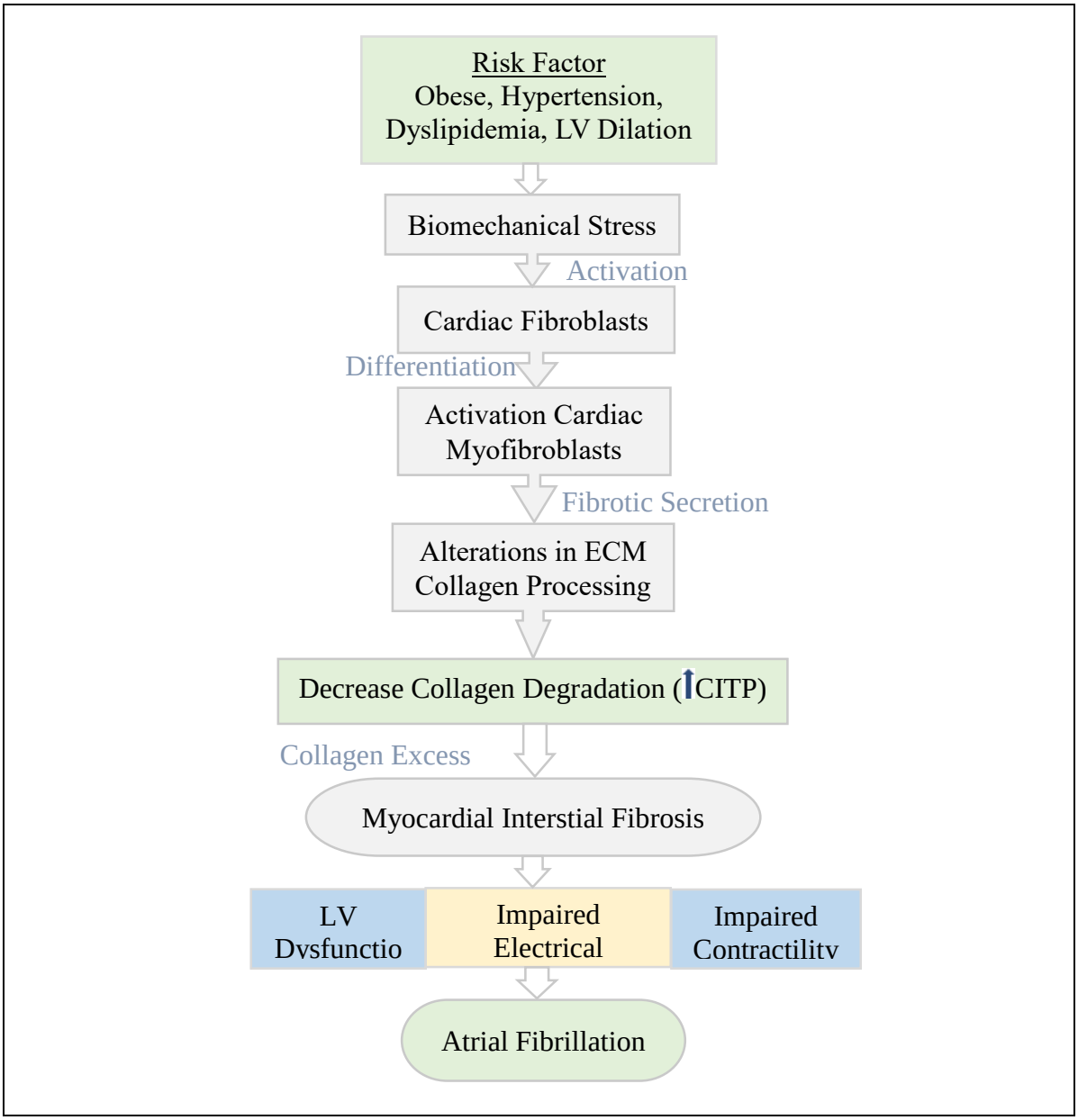
Demographic and clinical characteristics, measurement of body mass index according to the classified World Health Organization was also collected [29], as age and blood pressure (Bp) using a monitor and classified according to a report from the American Heart Association (AHA) task force on clinical practice guidelines [30].

2.3. THE STATISTICAL ANALYSIS

Information from the questionnaire and all test results from study group samples were entered into a data sheet. The data analysis for this work was generated utilising the social sciences statistical package, version 28.0 (IBM, SPSS, Chicago, Illinois, USA), and the real statistics resource pack software for Mac (Release 8.6) of the resource pack for Excel 2016, (Copyright, 2013 –2020). Descriptive statistics were applied to each group's data. Values were illustrated by n (%) for categorical; scale variables were presented by mean ± 2 standard deviation for normal data, while for non-normal data, continuous variables were presented by the interquartile range (IQR) and median. The distribution of the data was examined using the Shapiro-Wilk test as a numerical measure of normality. For abnormal distribution, the univariate analysis was performed using an independent Kruskal Wallis test for continuous variables.

The optimal threshold with high specificity and sensitivity for study cases was detected using receiver operating characteristic (ROC) analysis.

Central illustration representation of impaired turnover of type I collagen step in degradation that contributes to myocardial interstitial fibrosis in atrial fibrillation; Researcher Mustafa Hameed created the proposed illustration.



3- RESULTS

This study included 120 participants; the gender distribution was 78 females and 42 males; The age range of participants was between (22 – 90) years old and most of the participants were within the age group of >60 years; participants were divided into two groups: 60 of them were diagnosed with atrial fibrillation (AF) and 60 were used as a healthy control group. Patients were classified into subgroups according to disease duration to Group A: (12) with Paroxysmal AF. Group B: (13) with persistent AF, Group C: (22) with permanent AF and Group D: (13) with lone AF. The baseline characteristics of the comorbidity factors and medical history (hypertension, diabetes, hyperthyroidism and dyslipidemia) among AF patients were also collected. Results indicated that about 40% of the patient's groups had DM, only 15 % were reported having hypertension, 70% had hyperthyroidism, and 23 % were confirmed to have dyslipidaemia

The left ventricular (LV) diameter was measured in centimetres (*cm*) using echocardiography and classified according to a report from the American College of Cardiology (ACC). The group with moderate to severe dilation with a thick

wall in the left ventricular (LV) had a higher level of CITP than the group with mild dilation with a thick wall compared to the normal dilation as presented in Fig. 1

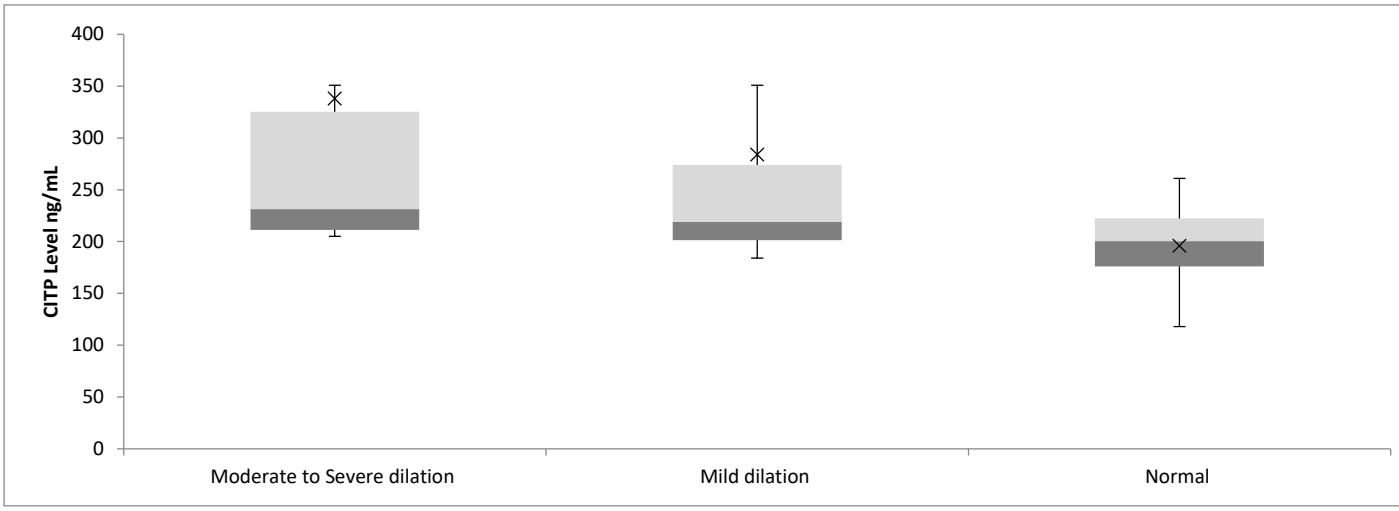


Figure-1: The mean differences in the biomarker CITP level based on the echocardiography findings in the case of atrial fibrillation

Multinomial logistic regression was performed and adopted to analyse the results level of CITP was examined. It was found that increased level of marker among AF patients represented independent significant risk factors in a severely dilated group (OR: 1.007; 95) % CI: (1.001-1.012), as shown in Table-1

Table-1: Associated factors of the dependent variable in AF patients compared to LV

Variable	Groups	OR (Lower – upper)	P value
CITP *ng/ mL*			
	Normal	1[a]	-
	Mildly Dilated	1.002(0.999-1.004)	0.183[NS]
	Moderately Dilated	1.000(0.993-1.007)	0.08[NS]
	Severely Dilated	1.007(1.001-1.012)	0.05[**S**]
p<0.05 considered significantly different**, [S]=** Significant**, [NS]=** Non-significant **1[a]**: reference category is normal			

Results of the receiver operating curve (ROC) curve and AUC analysis were performed to check CITP level as potential diagnoses markers of MIF in LV with AF cases. CITP level were shown to have a good diagnostic performance for prediction AF Patients compared to a healthy control group, data as presented in Table-2 and Figures-2.

CITP level showed a sensitivity =93.2%, specificity = 83.3% at a level of 165.5 *ng/mL*, PPV was 84.62%, NPV was 90.91%, and accuracy was 87.5%.

Interestingly, the diagnostic points of CITP level in predicting AF cases indicated a significant threshold a p-value of the AUC was <0.001 and Youden's J statistics of the parameters confirm these results.

Table-2: The ROC curve for the optimal threshold that assesses serum CITP for predicting MIF in LV

Biomarker	Cut-off Value	AUC %	CI (95%)	Sn. %	Sp. %	P-value	PPV %	NPV %	Accuracy %
CITP *ng/ mL*	165.5	0.829	0.741-0.917	93.2	83.3	<0.001[**S**]	84.62	90.91	87.5%

p<0.05 considered significantly different, [**S**]= Significant, [**NS**]= Non-significant
[**Sn**]= Sensitivity, [**Sp**]= Specificity, [**PPV**]= Positive Predictive Values, [**NPV**]= Negative Predictive Values, [**CITP**] = Carboxyterminal -Telopeptide of Type 1 Collagen

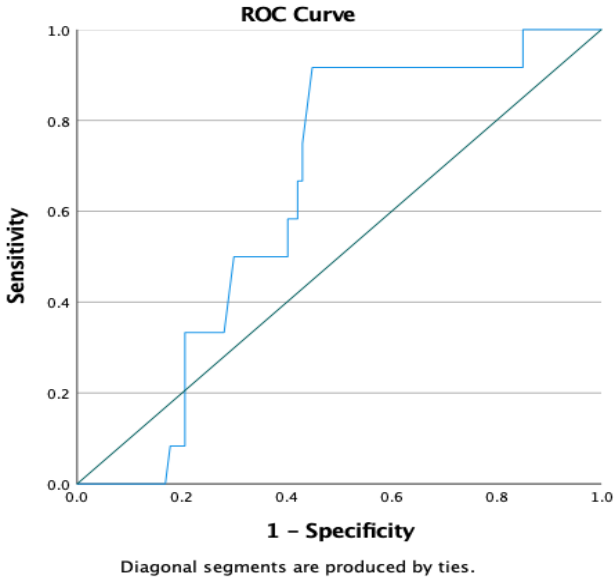


Figure-2: ROC curve for optimal diagnostic point analysis for predicting MIF in LV with AF patients using CITP

On the other hand, Table-3 and Figures-3, show the AUC and ROC for assessing LV diameter as a diagnostic marker of early-stage dilation with a thick wall in MIF among AF cases. The LV diameter produced an AUC of 0.683; P<0.001. The best cut-off value of LV for early dilation detection was 4.95*cm* with sensitivity and 86.7% and 81.7%, respectively, while the PPV was 65.28%, NPV was 72.92%, and accuracy was 68.33%.

Table-3: The optimal threshold ROC curve evaluating LV diameter for the diagnosis of early-stage dilation in MIF with AF cases

Echo Study	Cut off Value	AUC %	Cl 95%	Sn. %	Sp. %	P-value	PPV %	NPV %	Accuracy %
LV diameter *cm*	4.95	0.683	0.587-0.778	**86.7**	81.7	<0.001[**S**]	65.28	72.92	68.33%

[**P<0.05**] considered significantly different, [**S**]= Significant, [**NS**]= Non-Significant, [**Sn**]= Sensitivity, [**Sp**]=Specificity, [**PPV**]= Positive Predictive Values, [**NPV**]= Negative Predictive Values, [**AUC**]= Area Under the Curve, [**LV**]= Left Ventricular

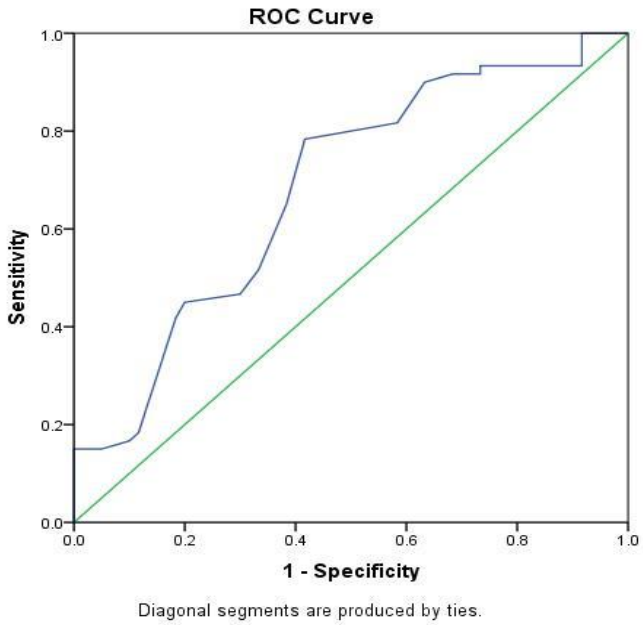


Figure-3: ROC curve for optimal diagnostic point analysis for predicting early-stage dilation in MIF with AF cases using LV diameter

Furthermore, Table-4 compares echo study parameter and clinical biomarker proposed from the cut-off values. The prognostic cut-off value of AF patients was highly significant in all comparisons.

Table-4: The sensitivity, specificity and accuracy cut-off values were used to compare the proposed clinical biomarker and the echocardiography study.

Groups	Parameters	AUC %	CI 95%	Sn. %	Sp. %	P-value	PPV %	NPV %	Accuracy %
Clinical Biomarkers Proposed	**S.C1TP** *ng/mL*	0.829	0.741-0.917	**93.2**	83.3	<0.001[**S**]	84.62	90.91	**87.5%**
Echo Study	**LV diameter** *cm*	0.683	0.587-0.778	**86.7**	81.7	<0.001[**S**]	65.28	72.92	**68.33%**

[**P≤0.05**] considered significantly different, [**S**]= Significant, [**NS**]= Non-Significant, [**Sn**]= Sensitivity, [**Sp**]= Specificity, [**PPV**]= Positive Predictive Values, [**NPV**]= Negative Predictive Values, [**P1CP**] = Carboxyterminal Propeptide of Type-1 Procollagen, [**C1TP**] = Carboxyterminal -Telopeptide of Type 1 Collagen, [**AUC**]= Area Under the Curve, [**LV**]= Left Ventricular

4- DISCUSSION

The current study aimed to investigate the association between the collagen deposition level of MIF and LV dilation with wall thickness among AF patients. The results indicate that most patients had moderate to severe dilation in the left ventricular (LV). At the same time, the cut-off value that depended on excess collagen deposition was directly related to the intensity of MIF and LV dilation with the thickness wall. Additionally, a study showed that increased serum CITP level were associated with hypertensive left ventricular fibrosis and diastolic dysfunction [31]. Furthermore, if this continues myocardial stress due to hypertension and other risk factors is thought to increase ECM deposition, leading to fibrosis that may compromise myocardial function and impair electrical conduction, favoring the advent of arrhythmias and HF; Collagen synthesis is a dynamic process involving metabolically active myofibroblasts [32].

Figure-1 showed that the parameter of the echocardiogram study classified left ventricular dilatation groups with a thick wall, and the mean predicted biomarker of these groups revealed highly significant differences between dilatation groups of left ventricular (LV) patients; the group with moderate to severe dilation in the LV with a thick wall had higher level CITP than the group with mild dilation with a thick wall, The result is in agreement with a study by Lombardi et al. showed that serum CITP level was elevated in patients with HCM [33]. However, it conflicts with a previous study report that found elevated serum markers of collagen metabolism at CITP concentrations in peripheral venous blood samples in patients with mild to moderate heart failure due to dilated cardiomyopathy (DCM). The reason is that myocardial stiffness or fibrosis is caused by increased collagen deposition, which increases CITP levels [34]**.**

The current study revealed that measuring serum CITP (at a cut-off value of > 165.5 *ng/mL*) were the best biomarker for distinguishing myocardium interstitial fibrosis (MIF) with atrial fibrillation (AF) patients from healthy groups (Table-2 and Fig. 2). results contribute to the theory of collagen deposition as a major mechanism involved in MIF in patients with atrial fibrillation. These results are consistent with previous studies showing that elevated CITP may facilitate the diagnosis or prognosis of myocardial fibrosis [35].

Also, this statement is corroborated **by López et al. (2015)** in their report. That is interpreted as serum CITP being the best biomarker for differentiating between patients and controls. Results also confirmed that left ventricular diameter has more sensitivity and specificity in early detecting co-extension of myocardial interstitial fibrosis (MIF) in atrial fibrillation patients (Table-3 & Fig. 3).

Table-4 show that the clinical biomarker proposed have higher sensitivity, specificity, and accuracy than echocardiography findings in the early detection of MIF in patients with atrial fibrillation. These results are consistent with previous studies showing that an echocardiographic study does not reliably identify myocardial fibrosis in patients with thickness wall cardiomyopathy. Still, it is reliably diagnosed by magnetic resonance imaging (MRI). An echocardiographic study may be useful in pre-identifying those who benefit from functional magnetic resonance imaging (fMRI) to confirm the finding of myocardial scarring. MRI: one of its advantages is its high diagnostic capacity, but it is time-consuming, expensive, requires intravenous contrast injection, and is only sometimes readily available. Therefore, echocardiographic studies cannot substitute for MRI [36]**.** That is interpreted as serum CITP being the best predictive biomarkers of myocardial fibrosis because both have a sensitivity of 93.2%, and a specificity of 83.3%, respectively. These biomarkers are inexpensive and readily available.

5. CONCLUSIONS

1. Serum CITP levels can indicate myocardial interstitial fibrosis in patients with atrial fibrillation.

2. Fibrosis represented by myocardial interstitial fibrosis and its risk factors significantly impacts serum CITP level, while serum lipid profiles alone have no significant impact.

3. Serum CITP level with a cutoff value greater than 165.5 *ng/mL* can be used as an alternative biomarker for patients with atrial fibrillation independent of myocardial interstitial fibrosis with a sensitivity of 93.2% and a specificity of 83.3%.

4. The majority of atrial fibrillation patients have myocardial interstitial fibrosis and comorbidities such as obesity and hypertension.

6. RECOMMENDATIONS

1. Studying the role of serum CITP level in the pathogenesis of atrial fibrillation will be needed to answer whether this role can be translated into therapeutic targets.

2. Study other biomarkers of collagen deposition like PICP, PIIICP, PINP, and PIIINP in a large sample size of patients with atrial fibrillation. So, this knowledge gives clinicians the ability to predict who will develop cardiomyopathy early and improve the prevention of this devastating disease.

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List of Abbreviations

ACC American College of Cardiology
ACC American College of Cardiology
AF Atrial Fibrillation
AHA American Heart Association
Bp Blood Pressure
CCU Cardiac Care Unit
CITP Carboxyterminal Telopeptide Type-I Collagen
DCM Dilated Cardiomyopathy
DM Diabetes Mellitus
ECG Electrocardiograms
ECM Extracellular Matrix
EF% Ejection Fraction Percentage
ELISA Enzyme Linked Immunosorbent Assay
ESC European Society of Cardiology
fMRI Functional Magnetic Resonance Imaging
HCM Hypertrophic Cardiomyopathy
HF Heart Failure
IQR Interquartile Range
LV Left Ventricular
MIF Myocardial Interstitial Fibrosis
OR Odds Ratio
PICP Carboxyterminal Propeptide of Type-1 Procollagen
PIIICP Carboxyterminal Propeptide of Type- III Procollagen
PIIINP Aminoterminal Propeptide of Type- III Procollagen
PINP Aminoterminal Propeptide of Type- I Procollagen
ROC Receiver Operating Characteristic

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