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RESEARCH

A novel prediction model for myocardial fibrosis in patients suspected of myocarditis

Miyokardit şüphesi olan hastalarda miyokardiyal fibrozis için yeni bir tahmin modeli

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Abstract

Purpose: This study aimed at establishing a predictive method that consists of clinical, electrocardiographic (ECG), and laboratory parameters for myocardial fibrosis, especially as detected on cardiac magnetic resonance imaging (CMRI), in patients examined with suspicion of myocarditis.

Materials and Methods: This study is a retrospective, single-centre study that includes patients admitted to our centre with suspected myocarditis between March 2020 and November 2023. Participants were categorised into two groups (myocardial fibrosis positive and myocardial fibrosis negative), and a detailed comparison of comorbidities, ECG changes, and laboratory parameters was performed. Multivariate analysis was conducted to identify independent predictors of myocardial fibrosis. A nomogram was constructed using the coefficients from the multivariate analysis to estimate the probability of myocardial fibrosis presence based on key predictors.

Results: This study included 98 participants with a median age of 30 years, predominantly male (80.6%), with 14.3% having hypertension, 8.2% having diabetes mellitus, and 10.2% being smokers. The myocardial fibrosis-negative group exhibited higher levels of left ventricular ejection fraction and lymphocyte count. Conversely, the myocardial fibrosis-positive group showed higher levels of ECG changes at admission, peak C-reactive protein (CRP), CRP velocity, peak troponin, N-terminal pro-brain natriuretic peptide (NT-proBNP), monocytes, and platelets (PLT). In multivariate analysis, PLT, lymphocyte, monocyte, peak troponin, and ECG changes were identified as independent predictors of myocardial fibrosis. Receiving operating characteristic (ROC) curve analysis showed the model's diagnostic accuracy for predicting myocardial fibrosis (area under the ROC (AUC): 0.959, 95% confidence interval (CI), and p<0.001).

Öz

Amaç: Bu çalışmanın amacı, miyokardit şüphesi ile tetkik edilen hastalarda özellikle kardiyak manyetik rezonans görüntülemede saptanan miyokardiyal fibrozisi klinik, elektrokardiyografik (EKG) ve laboratuvar parametrelerinden oluşan bir öngörücü metod ile saptamaya çalışmaktır.

Gereç ve Yöntem: Bu çalışma, Mart 2020 ile Kasım 2023 tarihleri arasında merkezimize şüpheli miyokardit ile başvuran hastaları içeren retrospektif, tek merkezli bir çalışmadır. Katılımcılar, miyokardiyal fibrosiz pozitif ve negatif olmak üzere iki gruba ayrıldı. Komorbid durumlar, EKG değişiklikleri ve laboratuvar parametrelerinin detaylı bir karşılaştırması yapıldı. Miyokard fibrozunun bağımsız belirleyicilerini tanımlamak için çok değişkenli analiz yapıldı. Çok değişkenli analizden elde edilen katsayılar kullanılarak miyokardiyal fibrosizin varlığını tahmin etmek amacıyla bir nomogram oluşturuldu.

Bulgular: Bu çalışma, yaş ortalaması 30 olan, %80.6'sı erkek, 98 katılımcıyı içermektedir. Hastaların %14.3'ünde hipertansiyon, %8.2'sinde diyabet varken %10.2'si sigara içicisiydi. Miyokardiyal fibrozis negatif grupta, sol ventrikül ejeksiyon fraksiyonu ve lenfosit sayısı daha yüksek oranlarda izlendi. Aksine miyokardiyal fibrozis pozitif grupta başvuruda EKG değişiklikleri, pik CRP, CRP velositesi, pik troponin, NT-proBNP, monosit ve trombosit (PLT) düzeyleri daha yüksek seviyelere sahipti. Çok değişkenli analizde PLT sayısı, lenfosit sayısı, monosit sayısı, pik troponin ve başvuru esnasındaki EKG değişiklikleri miyokard fibrozunun bağımsız belirleyicileri olarak saptandı. ROC eğrisi analizi, miyokardial fibrozisi tahmin etme modelinin doğru tanı koyma gücüne sahip olduğunu gösterdi. (AUC: 0.959, p<0.001).

Sonuç: Bu kapsamlı analiz, klinik ve laboratuvar parametreleri ile miyokard fibrozu arasındaki ilişkilere öngörüler sunarak, doğru tanı koyma oranına sahip bir tahmin modeli sunmaktadır.

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Conclusion: This comprehensive analysis highlights the relationships between clinical and laboratory parameters and myocardial fibrosis and presents a predictive model with high diagnostic accuracy.

Keywords:. Endomyocardial fibrosis, magnetic resonance imaging, myocarditis

Anahtar kelimeler: Endomiyokardiyal fibrozis, manyetik rezonans görüntüleme , miyokardit

INTRODUCTION

Myocarditis, which is characterised by inflammation of the myocardium, can arise from various sources, including infections, autoimmune diseases, or exposure to cardiotoxic substances. This inflammatory condition poses a significant risk, potentially leading to acute heart failure, chest pain, and severe arrhythmias, which can be life-threatening[1]. As inflammation resolves, the reparative processes often involve the replacement of damaged myocardial tissue with fibrous scar tissue. While this fibrotic response is a critical part of the healing mechanism, excessive or inappropriate fibrosis can lead to adverse outcomes, including impaired myocardial contractility, arrhythmias, and, ultimately, heart failure[2,3].

Understanding the mechanisms and predictors of myocardial fibrosis in the post-myocarditis period is essential for developing targeted therapeutic strategies to mitigate its detrimental effects and improve patient outcomes. Cardiac magnetic resonance imaging (CMRI) plays a pivotal role in the non-invasive assessment of myocardial fibrosis and provides valuable insights into the structural changes within the heart following myocarditis[4,5]. CMRI techniques, such as late gadolinium enhancement (LGE), enable the visualisation and quantification of fibrotic tissue in the myocardium with high precision. Myocardial fibrosis, often a consequence of inflammatory processes such as myocarditis, manifests as areas of increased signal intensity on LGE images, indicating the presence of scar tissue. By accurately delineating the extent and distribution of fibrosis, CMRI aids in risk stratification and prognostication for patients recovering from myocarditis[6,7]. Moreover, CMRI's ability to assess myocardial tissue characteristics, including the presence of oedema and inflammation, enhances its diagnostic utility in detecting and monitoring the progression of myocardial fibrosis. This non-invasive imaging modality not only contributes to the understanding of the underlying pathology but also guides therapeutic decisions and facilitates a more comprehensive approach to patient care[6-8].

Despite its numerous advantages, performing CMRI at the optimal time remains a challenge in many medical centres for patients suspected of myocarditis. Several factors contribute to this limitation. First, the cost associated with CMRI remains a hurdle for some centres, making it financially burdensome. Second, the lack of specialised practitioners who are capable of conducting optimal analyses adds to the challenges in effectively deploying CMRI. Third, accessing CMRI in the acute period is hindered by prolonged appointment times, preventing timely diagnosis and evaluation. Hence, cost-effective, readily available parameters with significant predictive capability may greatly assist clinicians in achieving a more precise diagnosis and forecasting the progression of individuals presenting with suspected myocarditis.

In addition to providing a comprehensive overview of myocardial fibrosis assessment techniques and challenges in current medical practice, this study aims to contribute novel insights into the prediction of myocardial fibrosis in patients suspected of myocarditis. By integrating data from ECG, echocardiography, and laboratory parameters, we seek to establish predictive models that can accurately estimate the presence and extent of myocardial fibrosis in these patients. Furthermore, this study hypothesizes that the combination of these multidimensional data sources will enhance diagnostic accuracy and prognostic capability, thereby facilitating more precise clinical decision-making and improving patient outcomes in the management of myocarditis.

MATERIALS AND METHODS

Study design and patient selection

This retrospective, single-centre study involved patients admitted to our centre with suspected myocarditis between March 2020 and November 2023. The study centred on patients aged 18 years and older with suspected myocarditis who underwent CMRI. Pre-diagnosis was determined as clinical suspicion if they met at least one admission and one diagnostic criterion, excluding detectable coronary

artery disease (≥50% stenosis) and known pre-existing cardiovascular or extra-cardiac conditions. A higher suspicion level was associated with meeting multiple criteria. In asymptomatic patients, at least two diagnostic criteria were required[9].

Clinical presentations included acute chest pain, pericarditic or pseudo-ischaemic symptoms, new-onset or worsening dyspnoea, fatigue, left/right heart failure signs, palpitations, unexplained arrhythmia, syncope, or aborted sudden cardiac death.

The diagnostic criteria comprised ECG/Holter findings (newly abnormal 12-lead ECG, atrioventricular block, bundle branch block, ST/T wave changes, ventricular arrhythmias, atrial fibrillation, etc.), markers of myocardial injury (elevated TnT/TnI), functional and structural abnormalities on cardiac imaging (echo/angiography/CMRI), and tissue characterisation by CMRI (oedema and/or LGE of classical myocarditis patterns).

Exclusion criteria included patients who did not meet the criteria for suspected myocarditis but met any of the following criteria: coronary artery disease (5), with known heart failure (10), congenital heart disease (7), stress-induced cardiomyopathy (4), recurrent myocarditis (3), pacemaker rhythm (4), severe heart valve dysfunction (3), segmental motility disorder (3), mechanical prosthetic heart valve (4) or use of anti-inflammatory therapy (5). Following exclusion, 98 patients were included in the final analysis. Demographic, laboratory, and clinical data were obtained from the hospital automation system. The study adhered to the ethical principles stated in the Declaration of Helsinki and received approval from the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (date: 31.01.2024; decision no.: 53). Given the retrospective nature of the study, the requirement to obtain written informed consent for each participant was waived.

The Başakşehir Çam and Sakura City Hospital has a dedicated focus on cardiovascular health and is equipped with advanced diagnostic tools, including CMRI facilities. The practices were carried out by a team of experienced medical professionals, including clinicians, researchers, and specialists, who possess expertise in the cardiology and radiology fields. The team conducted comprehensive evaluations of patients suspected of myocarditis, utilizing a combination of clinical assessments, laboratory investigations, and advanced imaging techniques such as CMRI. Overall, the study was conducted at a reputable institution by a competent team of healthcare professionals, utilizing state-of-the-art technology and robust analytical methods, thereby ensuring the reliability and validity of the findings.

Definitions and risk factors

The study collected information about several patient factors, including age, smoking status, and comorbidities. Diabetes mellitus (DM) was defined as the presence of at least one of the following conditions: use of blood glucose-lowering medications, fasting plasma glucose level equal to or greater than 126 mg/dL, or postprandial blood glucose level equal to or greater than 200 mg/dL[10]. Hypertension (HT) was defined as systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg or if patients were taking antihypertensive medication[11]. Echocardiographic evaluations were conducted by licensed physicians at the study clinic using a Hitachi ultrasound cardiovascular system (Arietta 65, USA) equipped with a 2.5–3.5 MHz transducer, following the recommendations for echocardiography[12]. The modified biplane Simpson's method was utilised to calculate the left ventricular ejection fraction.

CMRI analysis

We utilise a 1.5-tesla magnet (Philips Ingenia system Philips, Amsterdam, The Netherlands) in our centre. Technical aspects of scans are listed as follows: (i) breath control, steady-state free precession (SSFP) cine images with plans: horizontal-long axis (four-chamber), vertical-long axis (two-chamber), and the short axis with an 8-mm slice thickness without a gap in the T1 weighted sequence (short echo and repetition time) and a high flip angle (60–80 degrees). A high signal-to-noise ratio (SNR) is recommended (8). (ii) The phase-sensitive inversion recovery (PSIR) technique was utilised for the LGE scan 10 minutes after administration of the agent (Gadovist, Bayer Healthcare, Leverkusen, Germany) for each plan mentioned above. The Philips Intellispace portal version application (Philips Healthcare, Amsterdam, The Netherlands) was the utility that we used for function, mass, and quantitative LGE measurements. Function and mass were calculated with a fully automatic modality for the left ventricle and manual border delineation for the right ventricle. We separately measured the LGE positive myocardial

mass and percentage for 16 segments with both semi-automatic signal threshold and manual measurements.

Statistical analysis

Statistical analyses were performed using R statistical software (version 4.1.3, Vienna, Austria). The normality of variables was assessed using the Kolmogorov–Smirnov test, complemented by visual inspections of histograms and probability plots. Continuous variables were reported as mean ± standard deviation for normally distributed data and median (interquartile range $[IQR]_{25-75}$) for non-normally distributed data. Categorical data were presented as numbers and percentages. For group-wise comparisons of categorical variables, Fisher's exact test or the $\chi 2$ test was employed, while Independent Student's t-test and Mann–Whitney U tests were used to compare continuous variables between groups.

The parameters most associated with myocardial fibrosis were identified using the Boruta selection method (Figure 1), and specifically, confirmed attributes (CRP velocity, peak-troponin, ECG changes, NT-proBNP, lymphocyte, monocyte, and platelet count) and tentative attributes (current smoker and LVESV) with a Z-value higher than the feature from ShadowMax were further included in logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated in the multivariate regression analysis. Multicollinearity was examined using the variance inflation factor, with a threshold of >3 indicating significant multicollinearity. The Hosmer-Lemeshow test was utilized to evaluate the goodness-of-fit of logistic regression. In prediction models, rather than calculating traditional sample size, the event per variable rule of thumb was employed. Considering that the optimal ratio is >1/10, but may be >1/5 for rare diseases, all convenience sample were included in the study, with 53 events and 9 degrees of freedom (df). With 53/9 = 5.9, it was deemed that the model could be presented without significant overfitting risk, and therefore all available patients were included in the study.

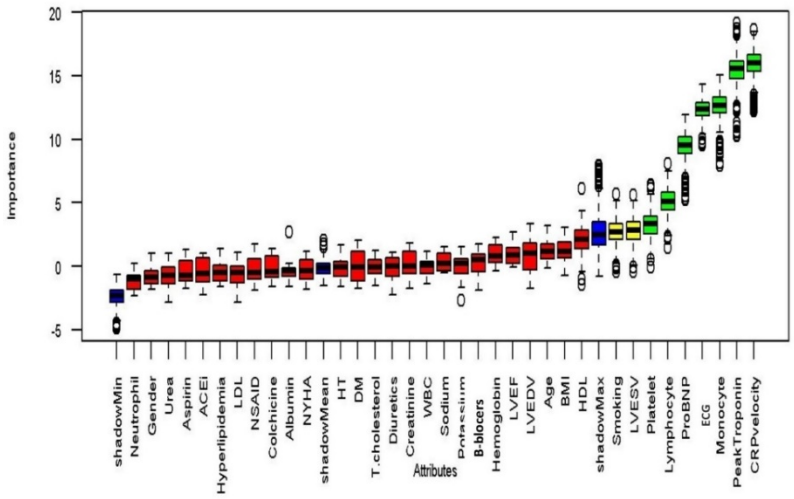

Figure 1. Boruta feature selection analysis to identify variables for subsequent regression analysis.

ACEIs, angiotensin-converting enzyme inhibitors; ASA, acetylsalicylic acid; CRP, C-reactive protein; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; NT-proBNP, N-terminal pro-b-type natriuretic peptide; LDL-C, low-density lipoprotein cholesterol; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic volume; NSAID, Nonsteroidal anti-inflammatory drugs; WBC, white blood cell.

Model performance was assessed using various criteria, including the Akaike information criteria (lower values indicating better fit), Brier score (lower values indicating better calibration), Adjusted R2 (higher values indicating better fit), and C-statistic (higher values indicating better discrimination). Non-linear relationships between log odds of myocardial fibrosis and related parameters were illustrated using restricted cubic splines with four knots. Receiver-operating characteristics (ROC) curve analysis was used to specify the discriminative capability of the regression model in determining myocardial fibrosis.

Correlation analysis of parameters associated with myocardial fibrosis was evaluated using the Spearman method. A risk prediction nomogram was developed based on determinants extracted from the multivariable regression model. Variable importance among the variables associated with myocardial fibrosis in the regression model was determined by the permutation-based random-forest method, ranking variables based on the Root Mean Squared Error metric. All statistical analyses utilized two-sided tests with a significance level (alpha) of 0.05.

RESULTS

Baseline characteristics

In the final analysis, the study included 98 participants with a median age of 30 (interquartile range (IQR)$_{25\text{-}75}$, 22–40) years, among whom 80.6% were male. Of the total CMRI scans, 53 (54%) patients exhibited myocardial fibrosis. The participants were divided into two groups: the first group consisted of those with myocardial fibrosis, and the second group included those without myocardial fibrosis. Comorbidities including DM, HT, hyperlipidaemia, and smoking showed similar prevalence between the two groups. Of the patients, 14.3% had HT, 8.2% had DM, and 10.2% were smoking. The group with positive myocardial fibrosis exhibited a higher rate of ECG changes at admission compared to the negative myocardial fibrosis group (52.8% *vs* 4.4%, $p<0.001$). Patients with positive myocardial fibrosis were also more likely to have a lower ejection fraction and lymphocyte count compared to those in the negative myocardial fibrosis group [ejection fraction: 59.5 (IQR$_{25\text{-}75}$, 53.0–65.5) *vs* 63 (IQR$_{25\text{-}75}$, 58.0–68.5), p=0.041; lymphocyte count: 2.04 (IQR$_{25\text{-}75}$, 1.30–2.61) *vs* 2.30 (IQR$_{25\text{-}75}$, 1.92–2.73), $p=0.018$]. Conversely, the group with positive myocardial fibrosis had higher levels of peak C-reactive protein (CRP), CRP velocity, peak troponin, NT-proBNP, monocyte count, and platelet (PLT) count ($p<0.05$ for all). Medications prescribed at discharge were comparable. Detailed demographic, clinical, and laboratory characteristics of the study population by the presence or absence of LGE involvement are presented in Table 1.

Independent predictors of myocardial fibrosis

In multivariate logistic regression analysis, PLT count (OR=1.01, 95% CI 1.01 [1.00–1.02], $p=0.048$), lymphocyte count (OR=0.31, 95% CI [0.10–0.94], $p=0.039$), monocyte count (OR=18.10, 95% CI [1.49–219], $p=0.023$), peak troponin (OR=1.25, 95% CI, [1.06–1.46], $p=0.007$), and ECG-change (OR=30.03,95% CI, [3.15–292.00], $p=0.003$) were determined as the independent predictors of myocardial fibrosis (Table 2).

We also developed a nomogram using the model and variable coefficient to estimate myocardial fibrosis (Figure 2). For instance, a patient diagnosed with myocarditis and HT with a PLT count of 300*10^9/L, lymphocyte count of 5*10^9/L, LVESV of 100 cm^3, monocyte count of 0.5*10^9/L, peak troponin value of 15 ng/mL, and no ECG changes, has a 29% likelihood of developing myocardial fibrosis according to the model.

Correlates of total myocardial fibrosis

The myocardial fibrosis had a positive correlation with peak-troponin, left ventricular end systolic volume (LVESV), monocytes, and PLT count but a negative correlation with lymphocytes ($p<0.05$ for all) (Figure 3). When the relative importance of each predictor in the model plot for myocardial fibrosis was analysed in the partial effect plot, peak-troponin was ranked as the most contributing predictor and PLT was ranked as the sixth most crucial variable (Figure 4).

Table 1. Baseline characteristics of the study population

Variables	Overall (n= 98)	Myocardial Fibrosis positive (n=53)	Myocardial Fibrosis negative (n=45)	*p*-value*
Demographic features and risk factors				
Age; Median, (IQR)	30 (22-40)	30 (23-43)	28 (21-37)	0.116
Male; n (%)	79 (80.6)	45 (84.9)	34 (75.6)	0.243
DM; n (%)	8 (8.2)	3 (5.7)	5 (11.1)	0.326
HT; n (%)	14 (14.3)	9 (17.0)	5 (11.1)	0.408
Hyperlipidemia; n (%)	42 (42.9)	23 (43.4)	19 (42.2)	0.907
Smoking; n (%)	10 (10.2)	3 (5.7)	7 (15.6)	0.107
BMI; kg/m^2; Median, (IQR)	24.5 (22.8-27.7)	26 (23.0-28.2)	23.8 (22.0-27.0)	0.565
ECG changes, n (%)	30 (30.6)	28 (52.8)	2 (4.4)	<0.001
Laboratory findings				
Total cholesterol, mmol/L; Median, (IQR)	3.9 (3.4-5.0)	3.98 (3.50-5.07)	3.96 (3.32-5.05)	0.724
Triglyceride, mmol/L; Median, (IQR)	1.43 (0.91-1.53)	1.46 (1.10-1.62)	1.22 (1.05-1.45)	0.455
HDL-C, mmol/L; Median, (IQR)	1.0 (0.81-1.22)	1.08 (0.78-1.19)	1.08 (0.91-1.37)	0.132
LDL-C, mmol/L; Median, (IQR)	2.4 (1.83-3.15)	2.46 (2.07-3.21)	2.38 (1.71-3.00)	0.320
Creatinine, mmol/L; Mean (SD)	0.84±0.16	0.86±0.15	0.82±0.17	0.274
Sodium, mmol/L; Mean (SD)	139±2.45	138.6±2.54	139.4±2.18	0.449
Potassium, mmol/L; Mean (SD)	4.1±0.7	4.38±0.38	4.32±0.45	0.119
NT-proBNP, pmol/L; Mean (SD)	591.1 ± 1201.6	916.2±1558	208.2±192.6	<0.001
Log (NT-proBNP); Mean (SD)	2.34±0.58	2.55±0.60	2.10±0.46	<0.001
WBC count, 10^9/L; Mean (SD)	10.8 (8.9-13.4)	10.9 (9.3-13.6)	10.8 (8.7-13.2)	0.450
Hemoglobin, g/L; Median, (IQR)	14.3 (13.2-15.1)	14.5 (13.7-15.4)	14.2 (12.5-15.0)	0.125
Platelet count, 10^9/L; Median, (IQR)	238 (205-294)	270 (214-314)	230 (204-270)	0.039
Lymphocyte count, 10^9/L, Median, (IQR)	2.14 (1.56-2.68)	2.04 (1.30-2.61)	2.30 (1.92-2.73)	0.018
Monocytes count, 10^9/L; Median, (IQR)	0.9 (0.7-1.3)	1.14 (0.82-1.79)	0.75 (0.57-1.01)	<0.001
Neutrophil count, 10^9/L; Median, (IQR)	7.8 (5.6-9.9)	8.3 (5.2-10.3)	7.6 (5.5-9.4)	0.179
Peak CRP, mg/L; Median, (IQR)	61.5 (13.5-116)	103 (59.2-150.8)	14.6 (4.2-42.7)	<0.001
CRPv, Median, (IQR)	0.7 (0.2-2.1)	1.73 (0.66-2.73)	0.21 (0.09-0.66	<0.001
Albumin, g/L; Median, (IQR)	43 (40-46)	43 (39-45)	44 (41-48)	0.215
Log (peak troponin); ng/mL, Median, (IQR)	3.3 (0.7-8.8)	6.5 (2.4-12.7)	1.3 (0.35-3.3)	<0.001
LVEF, %; Median, (IQR)	59.4 (52.5-67.2)	59.5 (53-65.5)	63 (58-68.5)	0.041
LVEDV, cm^3; Median, (IQR)	109.5 (83.75-122.0)	110 (88.5-124)	100 (75.0-118.5)	0.035
LVESV, cm^3; Median, (IQR)	42.5 (28.75-54.0)	48.2 (33.1-57.0)	34 (26.5-48.20)	0.012
Medications prescribed at discharge, n (%)				
B-blockers, n (%)	50 (51.0)	27 (50.9)	23 (51.1)	0.987
ACEIs or ARBs, n (%)	37 (37.8)	20 (37.7)	17 (37.8)	0.997
ASA, n (%)	28 (28.6)	15 (28.3)	13 (28.9)	0.949
NSAID, n (%)	6 (6.1)	3 (5.7)	3 (6.7)	0.836
Cholcium, n (%)	9 (9.2)	4 (7.5)	5 (11.1)	0.543

Values are presented as numbers (n) and percentages (%), mean±standard deviation, or median (interquartile range 25th-75th percentiles). p<0.05 was considered statistical significance.

ACEIs, angiotensin-converting enzyme inhibitors; *ARBs,* angiotensin receptor blockers; *ASA,* acetylsalicylic acid; *CRP,* C-reactive protein; *DM,* diabetes mellitus; *LGE,* late gadolinium enhancement; *HDL-C,* high-density lipoprotein cholesterol; *HT,* hypertension; *IQR,* interquartile range; *Log(NT-proBNP),* Logarithmic N-terminal pro b-type natriuretic peptide; *LDL-C*, low-density lipoprotein cholesterol; *LVEDV,* left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LVESV,* left ventricular end-systolic volume; *NSAID;* Nonsteroidal anti-inflammatory drugs; *WBC,* white blood cell

Table 2. Multivariable logistic regression analysis for predicting myocardial fibrosis

	OR⁺	**95% CI**	**p-value***
Smoking	0.09	0.01-1.18	0.067
Platelet count	1.01	1.00-1.02	**0.048**
Lymphocyte count	0.31	0.10-0.94	**0.039**
Monocyte count	18.10	1.49-219.00	**0.023**
CRP velocity	0.89	0.47-1.67	0.700
Log (NT-proBNP)	3.21	0.81-12.80	0.100
LVESV	1.03	1.00-1.07	0.056
Peak troponin	1.25	1.06-1.46	**0.007**
ECG changes	30.03	3.15-292.00	**0.003**

*p<0.05 was considered statistical significance. Abbreviations: CRP, C-reactive protein; OR, Odds ratio; LVESV, left ventricular end-systolic volume; Log (NT-proBNP), Logarithmic N-terminal pro-b-type natriuretic peptide.
⁺Model performance parameters: Adjusted R^2=0.773, Brier score= 0.083, C-statistic= 0.959, likelihood ratio chi-squared test=84.6.

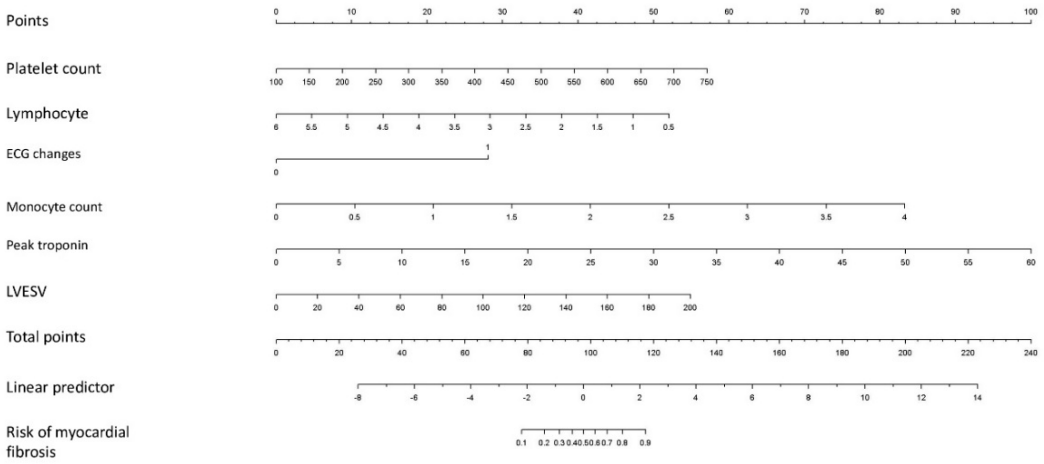

Figure 2. Nomogram for estimating the probability of myocardial fibrosis after myocarditis.
ECG, electrocardiography; LVESV, Left ventricular end-systolic volume.

In addition, Figure 5 illustrates the non-linear relationships between the log odds of myocardial fibrosis and certain laboratory and ECG parameters, all independently associated with fibrosis in the multivariate regression analysis. The regression model, as assessed by receiving operating characteristic (ROC) curve analysis, exhibited robust discriminatory power in predicting the probability of myocardial fibrosis (area under the ROC (AUC)=0.959, 95% confidence interval (CI), p<0.001) (Figure 6).

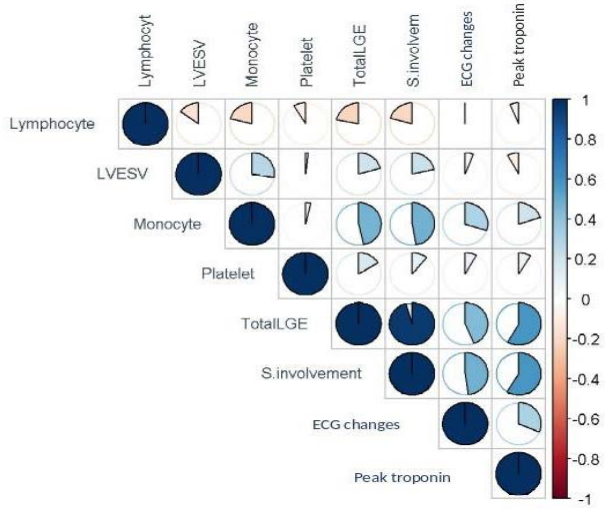

Figure 3. Spearman Correlation analysis of parameters associated with LGE.

ECG, electrocardiography; LGE, late gadolinium enhancement; LVESV, Left ventricular end-systolic volume, S involvement: Number of myocardial segments involved in LGE.

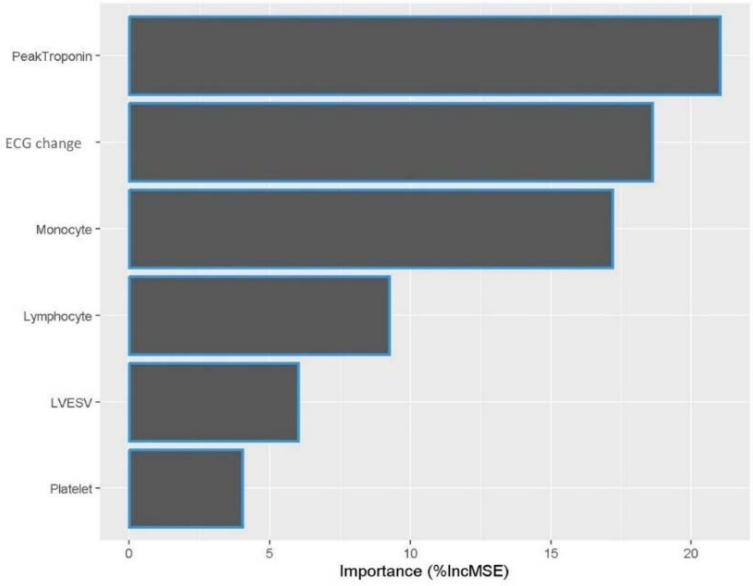

Figure 4. Partial effect plot of candidate predictors.

ECG, electrocardiography; LVESV, Left ventricular end-systolic volume

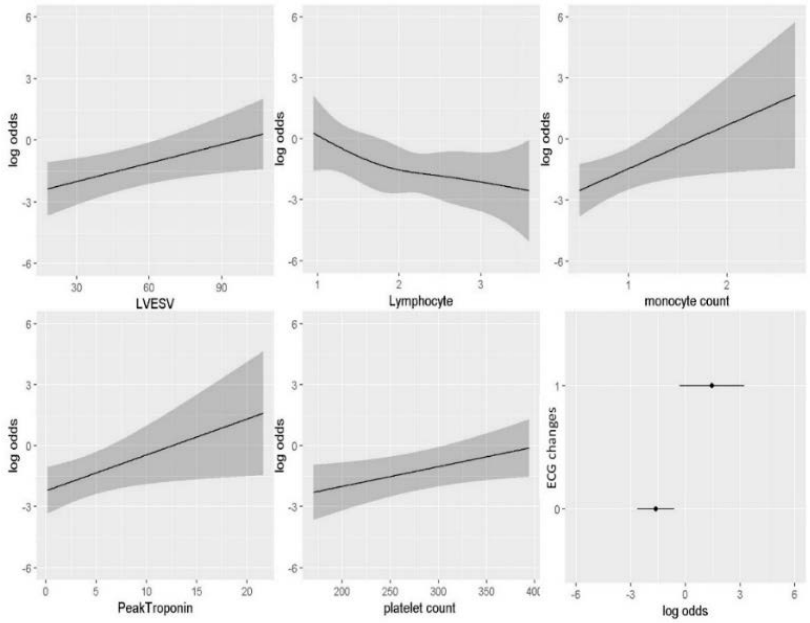

Figure 5. Restricted cubic spline analysis of myocardial fibrosis as a function of prediction parameters.

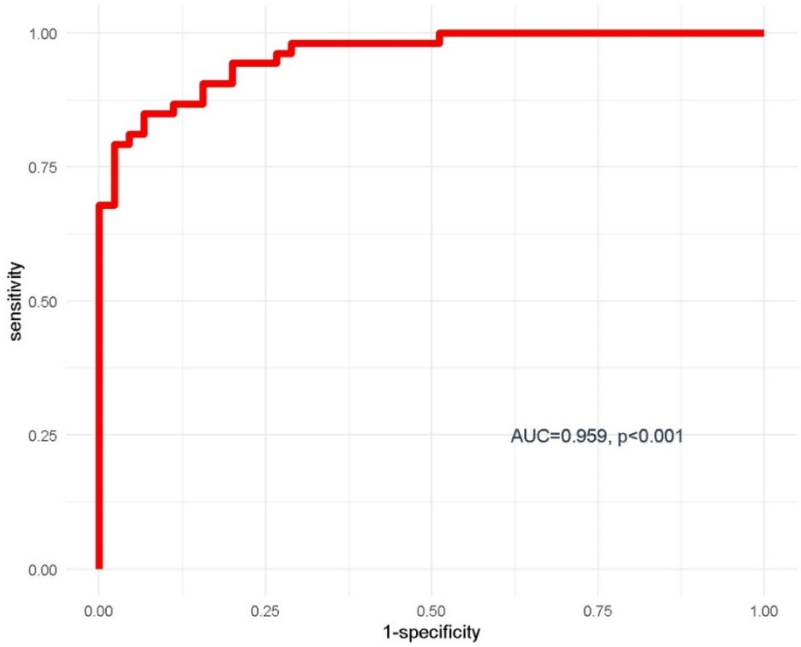

Figure 6. Receiver operating characteristic curve analysis. Abbreviation: AUC, area under the curve.

DISCUSSION

Our study revealed that peak troponin, ECG changes, and inflammatory markers have significant power in predicting myocardial fibrosis.

Myocarditis is an inflammatory condition that affects the myocardium, which is the muscular tissue of the heart. The pathophysiology of myocarditis is complex and involves a series of events triggered by various etiological factors, including infections (viral, bacterial, fungal, or parasitic), autoimmune reactions, toxins, or hypersensitivity reactions[2]. In response to the triggering factor, the immune system is activated, which involves the recruitment of immune cells, such as T lymphocytes, B lymphocytes, and macrophages, to the site of infection or inflammation in the myocardium. The immune cells play a central role in both combating the infectious agent and contributing to tissue damage through the release of inflammatory mediators. The immune response can directly target and damage cardiomyocytes [2,13,14]. Viruses may replicate within these cells, leading to their destruction. Additionally, cytotoxic T lymphocytes can recognise and attack infected cardiomyocytes[3,13,14]. The loss of functional myocardial cells compromises the contractility of the heart and contributes to cardiac dysfunction. Prolonged or severe inflammation can trigger fibrotic processes, leading to the deposition of collagen and extracellular matrix components in the myocardium. Myocardial fibrosis alters the normal architecture of the heart, impairing contractility and contributing to the development of heart failure[14,15,16]. In our study, we observed a significant alteration in inflammatory cell counts in response to this mechanism, which correlated with myocardial fibrosis. Additionally, we found that these are significant parameters influencing the risk rate of myocardial fibrosis in the nomogram.

Myocardial fibrosis represents a hallmark feature of myocarditis, reflecting the deposition of excessive extracellular matrix components in the cardiac tissue. This fibrotic remodelling has profound structural consequences, altering the architecture of the myocardium and potentially compromising cardiac function[17,18]. The development of myocardial fibrosis can result in impaired contractility, decreased compliance, and disrupted electrical conduction within the heart. These functional implications contribute to the onset of arrhythmias, heart failure, and other serious complications in patients with myocarditis[19-20]. The extent and severity of myocardial fibrosis often serve as valuable prognostic indicators of myocarditis. Studies have demonstrated a correlation between the degree of fibrotic involvement and adverse clinical outcomes, providing clinicians with crucial information for risk stratification and tailored patient management[18-20]. Detecting myocardial fibrosis early in the course of myocarditis can be challenging, as it may precede overt clinical manifestations. Advanced imaging techniques, such as CMR and positron emission tomography, play a pivotal role in identifying and quantifying myocardial fibrosis, enabling timely intervention and improved patient outcomes[23,24]. Recognising the importance of myocardial fibrosis opens avenues for targeted therapeutic strategies. Approaches aimed at modulating the fibrotic process, such as anti-inflammatory agents and antifibrotic drugs, may emerge as promising interventions to mitigate the long-term consequences of myocarditis and improve cardiac function. Therefore, early detection of myocardial fibrosis is important, as vigilant monitoring and treatments aimed at preventing fibrosis could mitigate irreversible damage.

Troponin and myocardial fibrosis are interconnected through the pathways of cardiac injury, inflammation, and remodelling. Elevated troponin levels can be both a consequence and contributor to myocardial fibrosis, reflecting the dynamic and complex nature of cardiovascular diseases[23-27]. The measurement of troponin levels has become a cornerstone in the diagnosis of myocarditis. Elevated troponin levels, indicative of myocardial injury, serve as a sensitive and specific marker for the presence of inflammatory processes affecting the heart. The diagnostic utility of troponin extends beyond the confirmation of myocarditis and aids in distinguishing myocarditis from other cardiac conditions presenting with similar symptoms, such as acute coronary syndromes. The extent of troponin elevation in myocarditis has notable prognostic implications[26,27,28]. Higher troponin levels often correlate with more severe myocardial injury and may serve as a prognostic indicator for adverse outcomes. Persistent elevation may signal ongoing inflammation and unresolved myocardial damage. Inflammatory insults to the myocardium cause cellular damage, leading to the leakage of intracellular components, including troponin, into the bloodstream. The degree of troponin elevation may reflect the intensity of the inflammatory response, offering insights into the

severity and extent of myocardial involvement[28,29]. Another important parameter reflecting myocardial involvement is ECG changes. ECG-changes comprise an essential tool in the evaluation of myocardial involvement, and ST-segment changes are frequently observed[30]. In this study, we observed a significant correlation between ECG changes and myocardial fibrosis in patients with myocarditis. ST segment changes, including elevation and depression, are frequently observed in the acute phase of myocarditis and may reflect the extent and location of myocardial inflammation. The presence of ECG changes during the acute phase of myocarditis may serve as early indicators of ongoing myocardial damage, contributing to the fibrotic remodelling observed in later stages. Consequently, the relationship between ECG changes and myocardial fibrosis in patients with myocarditis reveals the complex interaction between acute inflammation and long-term tissue remodeling[31].

Our study has several noteworthy limitations that warrant consideration. First, the retrospective nature and the confinement of the study to a single centre may compromise the generalisability of the findings. Second, the study's limitation lies in its relatively small sample size, which may restrict the robustness of statistical analyses. Therefore, a larger patient cohort could enhance the validity of the results. Despite these limitations, our study's findings offer crucial insights into the early-period risk of myocardial fibrosis.

In conclusion, we emphasises the significant predictive potential of peak troponin levels, ECG changes, and inflammatory markers in the detection of myocardial fibrosis among hospitalised individuals suspected of myocarditis. These findings may contribute valuable insights to the understanding of factors influencing myocarditis and pave the way for further research and clinical applications in predicting and managing myocardial fibrosis.

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