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Fragmented QRS complex, highly sensitive CRP, and fibrinogen in early detection of asymptomatic cardiac involvement in systemic lupus erythematosus

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Abstract

Background Patients with systemic lupus erythematosus (SLE) have an increased risk of developing cardiovascular illnesses. Asymptomatic affection might exist, so early diagnosis can improve the outcome.

Aim The purpose of this study was to determine the importance of highly sensitive C-reactive protein, fragmented QRS, and fibrinogen levels in identifying subclinical cardiac involvement in SLE patients, as well as how these variables relate to disease activity.

Results Regarding hs-CRP and fibrinogen, there were significant differences between the SLE and control group, with a higher frequency of fQRS in the lupus group. The lupus group was divided into 2 subgroups: 44 patients with fragmented QRS in ECG (83%) and 9 patients with normal QRS (17%) with a higher mean value of hs-CRP and fibrinogen level (58.76 ± 70.15, 18.54 ± 26.79) and low HDL (53.37 ± 10.37) in those with fQRS (+). The sensitivity and specificity of hs-CRP at a cut of level (3.5 mg/L) for fQRS in SLE patients were 75.5%, and 71.7%, respectively. Regression analysis showed hs-CRP and were significant predictors for fQRS changes in SLE patients.

Conclusions A more thorough evaluation of SLE patients with fQRS complexes with hs-CRP and fibrinogen is important with close follow-up for the detection of subclinical cardiac involvement in SLE. Also, SLE activity is linked to fQRS and fibrinogen. Therefore, we advise using them for additional medical care for lupus.

Key points

- Subclinical cardiac involvement in SLE patients.
- Fragmented QRS and fibrinogen associated with SLE activity.

Keywords SLE, Fragmented QRS complex, Hs-CRP, Fibrinogen, Asymptomatic cardiac

Background

Any organ may be impacted by systemic lupus erythematosus (SLE), a chronic systemic autoimmune illness with a heterogeneous etiology [1]. Major causes of morbidity and mortality in SLE patients include cardiovascular disease (CVD), which includes pericarditis, myocarditis, coronary artery disease, and endocarditis [2]. According to several researches, myocarditis and

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coronary artery disease (CAD) are both linked to SLE disease activity [3]. As lupus is an independent predictor of heart failure and asymptomatic cardiac affection might arise, patients with SLE are more likely than the general population to develop cardiovascular illnesses [4, 5]. Resting electrocardiography (ECG) is a cheap and simple noninvasive technology that can be utilized alongside laboratory indicators in SLE patients to assist in predicting cardiac events [6].

A useful indicator of myocardial scarring is the fragmented QRS (fQRS) complex, which is defined as extra spikes within the QRS complex. This marker can be used to detect myocardial scarring brought on by SLE-induced ischemia or inflammation and can be used to predict sudden death [1, 7]. Zigzag conductions around the myocardium that has been previously damaged by ischemia or inflammation may be the source of a fragmented QRS [8]. It helps locate myocardial scars, such as those brought on by cardiac sarcoidosis and CAD, identify high-risk patients with various cardiac conditions, and forecast sudden cardiac death [9]. According to earlier research, fQRS patients are much more likely to experience myocardial coronary perfusion abnormalities, and these abnormalities have a significantly higher prognostic value for cardiac death than non-fQRS patients [10, 11]. Additionally, it has been demonstrated that the fQRS complex functions as a predictive marker for LV dysfunction and microvascular reperfusion [12].

In patients with CAD diagnosed by myocardial single-photon emission tomography and cardiovascular magnetic resonance (CMR) imaging, fragmented QRS demonstrated great sensitivity and a strong negative predictive value for detecting myocardial scarring [13, 14]. Therefore, fQRS is effective for routine assessments of coronary artery disorders and myocardial damage in SLE patients.

Numerous laboratory indicators, such as highly sensitive C-reactive protein (hs-CRP) and fibrinogen level, which predict the progression to coronary artery disease, aid in the prediction of cardiac involvement in SLE patients [15]. The occurrence of fQRS in untreated SLE patients at the time of diagnosis has a connection to the disease activity and aids in subsequent immunosuppressive treatment. SLE activity is associated with elevated fibrinogen levels and hs-CRP levels greater than 3 mg/L, which predict coronary events [16].

Therefore, the current research aimed to identify the role of fQRS, hs-CRP, and fibrinogen levels in the detection of subclinical cardiac illness in SLE patients and their relation to SLE disease activity and to detect modifiable risk factors for favorable outcomes in SLE patients and postpone cardiac involvement.

Subjects and methods

Study design and setting

Between March and December 2022, a case–control study was carried out in the follow-up and inpatient units of the cardiovascular and rheumatology departments.

Study participants

All included SLE patients were above 16 years old and diagnosed according to Systemic Lupus International Collaborating Clinics (SLICC) revision of the American College of Rheumatology (ACR) classification criteria for SLE [17]. Patients with other rheumatic diseases; chronic diseases; cardiac diseases such as coronary artery disease, valvular heart disease, arrhythmias, congenital heart disease, and cardiomyopathies; cardiac symptoms; evidence of infection; or missed data from the medical records were excluded from the research.

Sample size and technique

Using online open Epi sample size calculation, this study was carried out on 53 SLE patients and 53 health controls according to the previous study of Hosonuma et al. [1]; the frequency of fQRS was 59% among SLE patients with confidence interval (CI) 95%. A simple random sampling technique was adopted for the selection of the participants.

Tools and instruments used in data collection

Information gathered from patient histories was found in the medical files of SLE patients who underwent a thorough examination and investigations while receiving follow-up care at the rheumatology department.

Operational steps

- Full history taking, general, musculoskeletal, and systemic examination.
- Lupus activity was assessed by SLEDAI-2 K [18]. Disease activity category grades were defined according to SLEDAI-2 K [19].
- ECG: All participants underwent a baseline 12-lead ECG (150 Hz low pass filter, 25 mm/s paper speed, 10 mm/mv voltage) to assess the presence of a fragmented QRS complex as an extra R wave or as notching in either the R or S waves in two contiguous leads corresponding to the territory of the coronary artery. Two seasoned cardiologists who were blinded to the patient characteristics and results assessed every ECG.
- All laboratory parameters included in SLEDAI-2 K were recorded, as well as blood sampling to measure fibrinogen level and hs-CRP level by BN ProsPec nephelometers [20], complete lipid profile, antiphospholipid antibodies, and all other laboratory investigations.

Statistical analysis

Statistical Package for Social Science (SPSS) (Version 20 Armonk, NY: IBM Corp) was used to analyze the data at a threshold of significance of 0.05. The mean, standard deviation (SD), and median interquartile range (IQR) were used to convey quantitative data, and absolute frequencies (number) and relative frequencies were used to express qualitative data (percentage). Unbiased samples while the Mann–Whitney *U* test was used for non-normally distributed variables, the Student *t*-test was employed to compare two groups of regularly distributed variables. Using the chi-square test, percentages of categorical variables were compared. To analyze the link between different study variables, Spearman's rank correlation coefficient was determined. To assess the validity, the 95% confidence interval (CI) was used to determine the sensitivity, specificity, predictive value for positive (PVP), predictive value for negative (PVN), and accuracy. All tests were two-sided. A *P*-value ≤ 0.05 was considered statistically significant (S), > 0.05 was considered statistically insignificant (NS), and *P*-value ≤ 0.001 was considered statistically highly significant (HS).

Results

A total of 106 participants were enrolled and were divided into 2 groups (53 SLE and 53 healthy controls). The mean age was 32.06 ± 8.89 years and 34.26 ± 8.83 respectively with female predominance in each group. Demographic data in SLE and control groups showed no significant difference. As regards the SLE group, the median of disease duration was 7 (4–12) years; the mean ± SD of SLEDAI was 9.11 ± 6.99, and the mean ± SD of 24-h protein ≥ 500 mg/24 h was 1236.39 ± 2291.93 (Table 1).

According to the distribution of the ECG leads and their anatomical interpretation, inferior wall affection, or right coronary artery affection, had the highest frequency of fQRS (39.6%), while anterior inferior lateral wall affection, or left coronary artery affection, had the lowest frequency (3.8%). By comparing mean ± SD between studied groups, there were statistically significant differences as regards hs-CRP ($p < 0.001$) and fibrinogen level (0.048), also with a higher frequency of f-QRS in ECG in the lupus group ($p < 0.001$) (Table 2).

The lupus group was divided into two subgroups: 44 patients with fragmented QRS in ECG and 9 patients with normal QRS with a higher mean value of hs-CRP and fibrinogen level (58.76 ± 70.15, 18.54 ± 26.79) and low HDL (53.37 ± 10.37) in those with f-QRS (+). However, there was no significant difference between SLE patients with fQRS and those with normal QRS in relation to total cholesterol, triglyceride, LDL, 24-h urinary protein, or antiphospholipid antibodies (Table 3).

Table 1 Demographic data, clinical and laboratory characteristics of the lupus group ($n = 53$)

Characteristics	Cases group $N = 53$	
Age (years)		
Mean ± SD	32.06 ± 8.89	
Gender, *N* (%)	Male 3 (5.7%)	Female 50 (94.3%)
Disease duration in years		
Mean ± SD	8.31 ± 4.93	
Median (IQR)	7 (4–12)	
Co-morbidity, *N* (%)	9	16.9%
Fever ≥ 38, *N* (%)	6	11.3%
Vasculitis, *N* (%)	2	3.8%
Inflammatory rash, *N* (%)	21	39.6%
Oral/nasal ulcers, *N* (%)	6	11.3%
Alopecia, *N* (%)	12	22.6%
Lupus Headache, *N* (%)	3	5.7%
SLE visual disturbance, *N* (%)	4	7.5%
Arthritis, *N* (%)	31	58.5%
Low complement, *N* (%)	10	18.9%
Urinary pus cells, *N* (%)	5	9.4%
24-h urinary protein ≥ 500 mg/24h		
Mean ± SD	1236.39 ± 2291.93	
Median (IQR)	193 (121–1521.25)	
SLEDAI score (105)		
Mean ± SD	9.11 ± 6.99	
Median (IQR)	8 (4–15)	

SD standard deviation, *IQR* interquartile range, *SLEDAI* Systemic Lupus Erythematosus disease activity index

Table 4 shows a highly significant difference between different grading of SLEDAI and fibrinogen level with the highest level in high and very high active patients (34%, 25%) and the highest frequencies of fQRS in mild (100%) next moderate (94.1%) active lupus subjects. Also, no significant difference regarding hs-CRP was shown. According to the Roc curve, the sensitivity of hs-CRP at cut-off = 3.5 mg/L for detection of fQRS was 75.5%, specificity was 71.7% with 95%CI = (0.669–0.855), and AUC was 0.762, $p < 0.001$ (Fig. 1a). Otherwise, the sensitivity of fibrinogen g/l at cut-off = 2.75 as a marker for fQRS in the SLE group was 62.3%, specificity was 56.6% with 95%CI = (0.495–0.713), and AUC was 0.604, $p < 0.001$ (Fig. 1b). It was found a significant positive correlation between fibrinogen g/L and LDL $r = 0.275$ and $p < 0.05$. Also, there was a significant positive correlation between fibrinogen g/L and SLEDAI score $r = 0.538$ and $p < 0.001$.

In Table 5's Cox regression analysis, HDL and hs-CRP were found to be significant predictors of fragmented QRS alterations in SLE patients with C.I. (1.1–1.35, 1–1.574).

Table 2 Fragmented QRS, fibrinogen, and hs-CRP of the studied groups ($n=106$)

Characteristic	Cases group $N=53$		Control group $N=53$		Z	χ^2	P value
Hs-CRP mg/L					−4.648		< 0.001**
Mean ± SD	22.02 ± 40.85		4.64 ± 8.49				
Median (range)	5.3 (3.4–13.8)		1.9 (1.37–4)				
Fibrinogen g/L					−1.850		0.048*
Mean ± SD	16.15 ± 25.13		6.41 ± 8.83				
Median (range)	3.1 (2.1–23)		2.5 (1.99–3.2)				
Fragmented QRS	***N***	**(%)**	***N***	**(%)**		[a]41.153	< 0.001**
(+) fQRS	44	83	11	20.8			
(−) fQRS	9	17	42	79.2			

SD standard deviation

* Significant $P \leq 0.05$

** Highly significant $P \leq 0.001$

[a] Chi-square test (χ^2). *hs-CRP* high-sensitivity C-reactive protein, *fQRS* fragmented QRS

Inter-and intra-observer variabilities using the Bland–Altman test were non-significant ($p=0.17$ and 0.38; respectively).

Discussion

SLE is an independent predictor of heart failure, and SLE patients are at much higher risk for cardiovascular involvement than the general population [1]. In the current study, we found that fQRS are significantly detected in the SLE patients compared to the control group which presented in 83% of the patients and only 20.8% of the controls with $P<0.001$ in agreement with research by Hosonuma et al., which discovered that 59% of SLE patients had fQRS at the time of diagnosis [1]. Also, Mavrogeni et al. observed fQRS in 63% of SLE patients who were untreated [21] and Bayar et al. found that the prevalence of fQRS was higher in patients with rheumatic diseases including SLE than in controls [15].

However, another study on fQRS in SLE patients following treatment interventions found that the fQRS rate was lower, at 41% than in the present study [8]. The elimination of fQRS with the start of therapy may be the cause of these variations in outcomes.

The present study shows that the hs-CRP level was higher in SLE patients having fQRS than in SLE patients with normal QRS as also detected in the study of Demir et al. [8]. In patients with stable angina pectoris, Cetin et al. found an association between fQRS and CRP levels and proposed that fQRS was independently related to systemic inflammation [22]. Additionally, Cetin et al. demonstrated a correlation between fQRS and an elevated hs-C reactive protein level, suggesting that the development of fQRS in CAD patients may be associated with systemic inflammation. Microvascular dysfunction is frequently the outcome of an inflammatory response mediated by an oxygen-free radical [23].

Also, there was a higher mean value of fibrinogen in SLE patients with fragmented QRS than SLE patients with normal QRS, in agree, elevated fibrinogen levels were linked to a higher risk of hypercoagulability state and developing heart disease in a study of more than 1.3k individuals [24]. In addition, a significant difference between SLE patients with (+) fQRS and HDL showed lower mean values ± SD of HDL (53.37 ± 10.37) than SLE patients with normal QRS. Regarding LDL and triglycerides, there were no statistically significant differences between fQRS (+) SLE patients and SLE patients with normal QRS.

This study did not find any statistically significant difference between fQRS changes and proteinuria in SLE patients. However, there was a higher mean value ± SD of proteinuria in SLE patients with fQRS (1372.28 ± 2478.58) than those with normal QRS. A significant risk of nephritis was also observed in SLE patients with fQRS, according to Hosonuma et al. In situ, immune complexes (ICs) may play a role in an immunological mechanism that explains this association [1].

Current results showed a significant correlation between fQRS and the various score grading of the SLE activity, where the SLEDAI-2K was significantly higher for SLE patients in the fQRS group than those in the normal QRS group. This was also detected in other studies [1, 8]. As a result, we believe that increased myocardial involvement from SLE disease activity justifies the relevance of fQRS to SLEDAI-2K, which can thoroughly assess systemic organ damage mediated by immunological mechanisms.

In this research, the SLE patients had higher hs-CRP levels than healthy individuals. These results are consistent with research done on various SLE groups in other

Table 3 Relation of fragmented QRS changes with different SLE patient's characteristics ($n=53$)

Characteristics	ECG QRS changes				*Z*	χ^2	*P* value
	Fragmented QRS ***N*** **= 44**		**Normal QRS** ***N*** **= 9**				
Disease duration in years					− 0.246		0.806
Mean ± SD	8.45 ± 5.16		7.67 ± 3.97				
Median (IQR)	7.5 (4–12)		7 (4.5–11)				
Triglyceride mg/dL					− 0.913		0.361
Mean ± SD	130.99 ± 77.09		150.49 ± 90.63				
Median (IQR)	106 (73–179.25)		123 (80.25–180)				
Total cholesterol mg/dL					− 0.320		0.749
Mean ± SD	173.06 ± 40.06		160.51 ± 51.76				
Median (IQR)	167 (146.8–201)		188 (106.8–192)				
HDL mg/dL					− 2.503		0.012*
Mean ± SD	53.37 ± 10.37		65.55 ± 107.08				
Median (IQR**)**	56 (52.25–59.1)		45 (37–49)				
LDL mg/dL					− 0.036		0.972
Mean ± SD	125.17 ± 77.44		154.58 ± 149.4				
Median (IQR)	116 (76.5–151.4)		99 (81.5–143.3)				
24-h protein ≥ 500 mg/24h					− 0.439		0.661
Mean ± SD	1372.28 ± 2478.58		572.04 ± 724.79				
Median (IQR)	168.5 (121–1876.5)		180 (115–1072.2)				
Hs-CRP mg/L					− 3.031		0.003*
Mean ± SD	58.76 ± 70.15		14.51 ± 27.6				
Median (IQR)	8.63 (2.6–85)		5.2 (3.3–10)				
Fibrinogen g/L					− 2.881		0.004*
Mean ± SD	18.54 ± 26.79		4.43 ± 7.73				
Median (IQR)	3.2 (2.3–31)		2.1 (1.3–2.6)				
APL antibodies	***N***	**(%)**	***N***	**(%)**		[a]0.267	0.605
Positive	11	25	3	33.3			
Negative	33	75	5	66.7			

SD standard deviation, *IQR* interquartile range, *APL antibodies* antiphospholipid antibodies, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

* Significant $P \leq 0.05$

[a] Chi-square test (χ^2)

Table 4 SLEDAI score grading in relation to fragmented QRS changes, fibrinogen, and hs-CRP of the SLE group ($n=53$)

Characteristics	SLEDAI grading										[a]χ^2	*P* value
	No activity		**Mild**		**Moderate**		**High**		**Very high**			
Hs-CRP mg/L Median (IQR**)**	91 (2.77–164)		5.22 (4.9–10.2)		6.32 (2.14–35)		3.85 (2.9–9.74)		5.63 (2.28–9.5)		3.474	0.482
Fibrinogen g/L Median (IQR)	1.5 (1.35–2.25)		2.9 (2.3–2.9)		3.1 (2.15–13)		34 (3–69)		25 (3.5–52)		22.397	< 0.001**
Fragmented QRS	***N***	**(%)**	***N***	**(%)**	***N***	**(%)**	***N***	**(%)**	***N***	**(%)**	19.509	< 0.001**
(+)f QRS	3	33.3	7	100	16	94.1	12	92.3	6	85.7		
(−)f QRS	6	66.7	0	0	1	5.9	1	7.7	1	14.3		

SLEDAI Systemic Lupus Erythematosus Disease Activity Index

[a] Chi-square test (χ^2)

** Highly significant $P \leq 0.001$

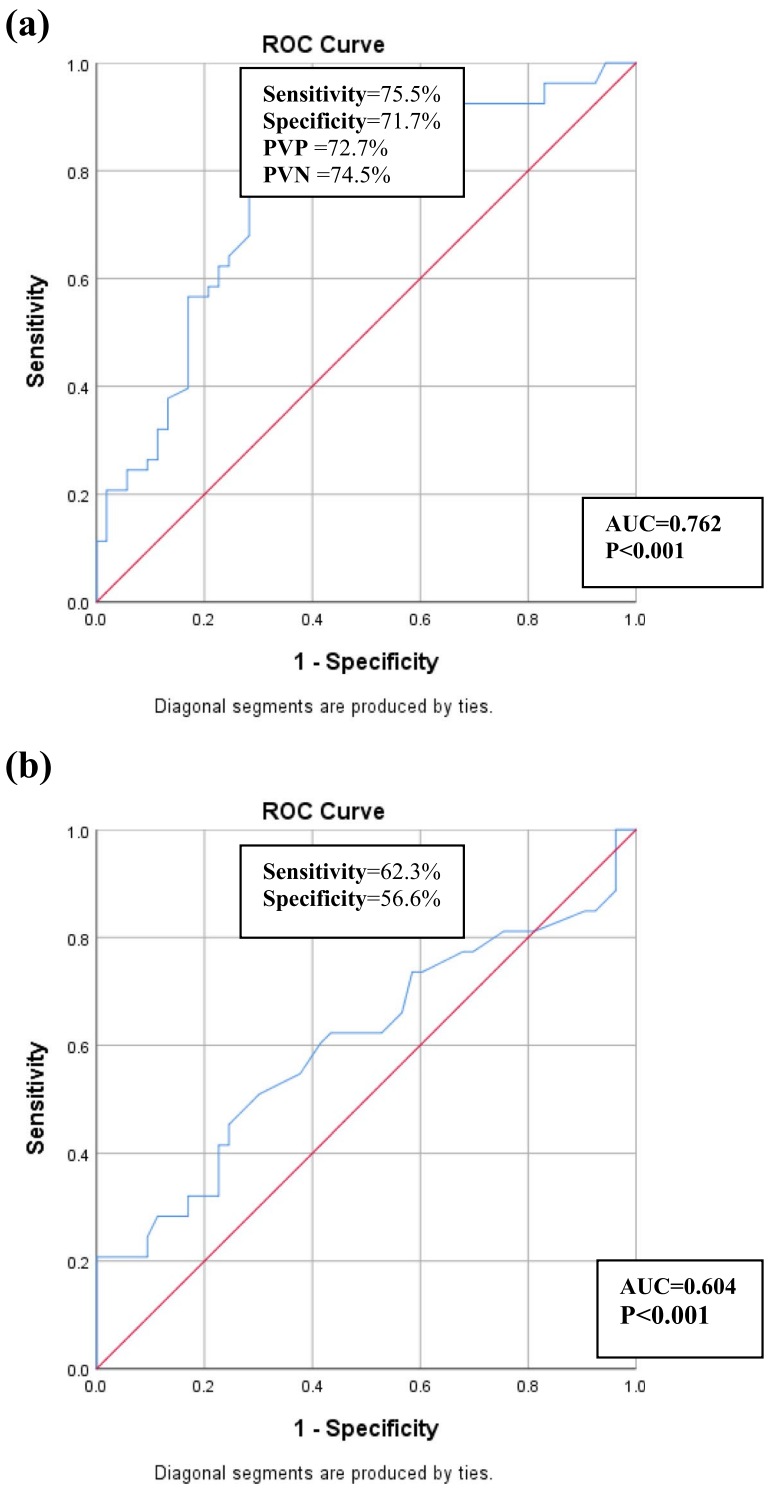

Fig. 1 **a** Validity of hs-CRP mg/L at cut off at 3.5 for detection of fQRS within the SLE group with 95%CI = 0.669–0.855, predictive value for positive (PVP) = (72.7%), predictive value for negative (PVN) = (74.5%), and (73.6%) accuracy. **b** Validity of fibrinogen g/L at 2.75 cut off for fQRS detection within SLE group with 95%CI = 0.495–0.713, predictive value for positive (PVP) = (58.6%), predictive value for negative (PVN) = (60%), and (59.4%) accuracy

Table 5 Cox regression of QRS changes in ECG changes in SLE patients ($n=53$)

Variables	B	S.E	Wald	Sig	Exp(B)	95% C.I. for EXP(B)	
						Lower	Upper
Hs-CRP mg/L	0.013	0.011	1.554	**0.032***	1.213	1.1	1.35
Fibrinogen g/L	−0.047	0.060	0.614	0.433	0.954	0.848	1.074
HDL	0.227	0.116	3.814	**0.048***	1.254	1	1.574

B beta coefficient, *SE* standard error. Wald, the name of the test

* Significant $P \leq 0.05$

studies [25]. Some studies, however, found no changes in CRP levels between SLE patients and the general population or even found that SLE patients had lower CRP levels than healthy people [26]. These results imply that the increased production of IFN-α, which is characteristic of active SLE and inhibits CRP formation, is the mechanism causing reduced CRP production [16].

We found that there was no statistically significant difference or correlation between different SLEDAI score grading and hs-CRP in lupus patients. According to Enocsson et al., IFN- downregulates CRP expression, and the rs1205 CRP polymorphism may account for the low basal CRP and insufficient CRP responses among individuals with active SLE [27].

In agreement with the findings of Litvinov et al. [28], we found a statistically significant increase in the mean fibrinogen value in the SLE group compared to the control group. Also, there was a significant positive correlation between SLEDIA and fibrinogen. Fibrinogen is one of the acute-phase proteins; its synthesis is elevated during injury and inflammation and is closely associated with SLEDAI raising the risk of hypercoagulability and heart diseases [29, 30]. These results were in agreement with that discussed in the study of Liang et al., who found that hypercoagulability and elevated fibrinogen levels were related to active disease and elevated ESR in SLE [31].

In the present study, there was a significant positive correlation between fibrinogen and LDL in SLE patients in agreement with Serban et al., who noticed a positive correlation between fibrinogen and LDL [32]. According to the ROC curve, hs-CRP was a significant detector for QRS changes in ECG in SLE patients at the cut-off levels of serum hs-CRP (≥3.5 mg/L); similarly, Pesqueda-Cendejas et al. had found that a significant cardiovascular risk and high clinical activity in SLE were both associated with serum CRP levels (≥3 mg/L) [16].

Regression analysis for the current study showed that hs-CRP and HDL were significant predictors for QRS complex changes in SLE patients in accordance with two studies that had reported a significant link between CAD, hs-CRP, and dyslipidemia including low HDL in the SLE patients with certain cardiovascular risk factors [27, 33]. So, hs-CRP could serve as a surrogate marker for cardiovascular risk in SLE patients.

All these findings support that as the inflammation increased, there is a harmonious increase in fQRS, fibrinogen level, and hs-CRP level, and as the activity increased, there is an increase in fQRS and fibrinogen level in SLE patients. So, be anxious about cardiac events occurring despite the absence of cardiac symptoms.

Limitations

This study had some limitations. It is a single-center study and has a small sample size; also the effects of treatment were not studied; this should be investigated in future research. Nevertheless, multicenter prospective studies are needed to verify our results.

Conclusions and recommendations

Fragmented QRS complexes are more frequent in patients with SLE and high fibrinogen and hs-CRP levels are significantly associated with fQRS in SLE patients. These findings may indicate subclinical cardiac involvement in SLE. So, it is reasonable to evaluate patients with SLE with fQRS complexes more in detail. Fragmented QRS and fibrinogen level associated with SLE activity. So, we recommend their use for follow-up with treatment.

Abbreviations

ACR	American College of Rheumatology
CAD	Coronary artery disease
CMR	Cardiovascular magnetic resonance
ECG	Electrocardiogram
FQRS	Fragmented QRS complex
HDL	High-density lipoprotein
Hs-CRP	Highly sensitive C-reactive protein
IFN	Interferon
ICs	Immune complexes
LDL	Low-density lipoprotein
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus disease activity index 2000
SLICC	Systemic Lupus International Collaborating Clinics

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Authors' contributions
All authors contributed and shared in the writing process.

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Availability of data and materials
We approve the availability of our data upon request.

Declarations

Ethics approval and consent to participate
An official permission was obtained from Institutional Review Board NO. (ZU-IRB # 9203-20-2-2022) at the Faculty of Medicine, Zagazig University Hospitals, and from the Rheumatology & Rehabilitation and Cardiovascular Departments at the same University. The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1964) for studies involving humans. A written informed consent was obtained from the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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