ORIGINAL ARTICLE

Comparison of the Incidence of Fragmented QRS Complex on Electrocardiogram in Patients with Connective Tissue Disorders and Healthy Individuals

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ABSTRACT

Objective: To compare the incidence of fragmented QRS complex in electrocardiograms in patients with connective tissue disorders compared to healthy individuals.

Study Design: Cross-sectional comparative study.

Place and Duration of Study: This study was conducted at the Department of Medicine, Combined Military Hospital (CMH), Multan, Pakistan from February 2024 to July 2024.

Methods: A total of 30 patients aged≥ 18 years and diagnosed with various connective tissue disorders were recruited in the study group (named CTD group). Another 30 individuals aged≥ 18 years or older without any known connective tissue disorders were added to the Control group. A standard 12-lead electrocardiogram was performed for each participant at rest, and the incidences of fragmented QRS complexes were recorded. The primary outcome of the study was to compare the incidence of fragmented QRS complex in patients with connective tissue disorders compared to healthy individuals by applying the Chi-square test. Results in the CTD group were also stratified by using independent t-tests and a Chi-square test for continuous and categorical variables, respectively. A $P<0.05$ is considered significant in all the comparisons.

Results: The mean age of study participants was 41.88±8.7. Female patients comprised 70% of the study population, and males comprised 30%. The results of the primary outcomes of the study showed that a significantly higher number of patients had a fragmented QRS complex in the CTD group compared to the Control group (56.66% vs 6.66%, respectively, $P=<0.0001$). The stratification of the incidences with the clinical variables in the CTD group established its significant association with age ($P=0.024$) and duration of the disease ($P=0.048$).

Conclusion: A significantly higher incidence of fragmented QRS complexes is present in patients with connective tissue disorders compared to the normal population.

Keywords: *Connective Tissue Diseases, Electrocardiography, Incidences, QRS Complex.*

How to cite this: *Wajid H, Barki WH, Batool S, Hashmi Z, Shafiq A, Pirzada HZ. Comparison of the Incidence of Fragmented QRS Complex on Electrocardiogram in Patients with Connective Tissue Disorders and Healthy Individuals. Life and Science. 2025; 6(2): 248-254. doi: http://doi.org/10.37185/LnS.1.1.796*

Introduction

Connective tissue disorder (CTD) encompasses a diverse group of autoimmune diseases characterized by abnormalities in the connective tissues throughout the body, which provide structural and functional support to various organs and systems within the body. CTD, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), Sjogren's syndrome, polymyositis, and dermatomyositis, leads to chronic inflammation and immune system dysregulation, which can cause widespread tissue damage and organ dysfunction and often involves multiple organ systems. With cardiovascular involvement, CTD is a significant source of morbidity and mortality in these

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Received: Aug 31, 2024; Revised: Jan 12, 2025
Accepted: Jan 22, 2025

patients.[1,2]

CTD is a rare condition with uncertain global incidence and affects all races with similar clinical manifestations across ethnic groups. A 2022 Manhattan-based population study revealed new epidemiological data, which shared the prevalence of CTD as 2.98 per 100,000, with an incidence of 0.39 per 100,000. CTD predominantly affects women, with a 3.3:1 female-to-male ratio. A Norwegian study reported an incidence of CTD as 2.1 per million yearly and a mean diagnosis age of 37.9 years. These findings provide an updated perspective on CTD's frequency and demographic distribution in an urban setting.[1,3]

The heart is particularly susceptible to the inflammatory and fibrotic processes inherent in CTD, which are presented in the shape of multifaceted cardiovascular (CV) complications. These include pericarditis, myocarditis, myocardial fibrosis, valvular heart disease, and accelerated atherosclerosis. This range of manifestations highlights the complex interplay between CTDs and cardiac health, emphasizing the need for comprehensive CV assessment and management in patients with these disorders. Despite advances in treatment modalities, cardiac complications remain a significant cause of mortality in patients with CTDs, underscoring the critical need for early detection and intervention.[4]

Fragmented QRS (fQRS) on an electrocardiogram (ECG) indicates myocardial scarring and conduction issues, often linked to structural heart disease. It features an extra R' wave or notching in the R or S wave within a narrow QRS complex. fQRS is associated with cardiac conditions like ischemic heart disease (IHD), cardiomyopathies, and ventricular arrhythmias, and is also significant in systemic diseases such as CTDs.[5] Myocardial fibrosis, which is commonly seen in CTD, can lead to arrhythmias, heart failure, and sudden cardiac death. Fibrosis disrupts the heart's conduction system, contributing to fQRS development. Due to the systemic impact of CTDs on the heart, fQRS may occur more often in these patients than general population. This cardiac involvement is, however, frequently underdiagnosed, especially early on, as symptoms can be absent or nonspecific.[6]

Cardiac involvement in CTDs often develops insidiously, evading detection by traditional biomarkers and imaging methods. fQRS, a marker of myocardial fibrosis, may serve as a valuable non-invasive tool for the early detection of cardiac involvement in CTD patients, potentially enabling timely intervention and improved outcomes.[7,8]

However, the role of fQRS in CTDs is not well-established, and there is a paucity of comprehensive data comparing its incidence across multiple CTDs and with the normal population. If proven reliable, fQRS might offer a simple, cost-effective screening tool for cardiac involvement in CTDs, enhancing early detection and patient care.

Further research is therefore required to understand the prevalence of fQRS in CTD patients especially in our local population. This study aims to determine if CTD patients have a higher incidence of fQRS compared to the general population. The results of this study will have important implications for cardiac screening and management of patients with CTD, potentially leading to improved outcomes through earlier detection and intervention.

Methods

This comparative cross-sectional study was carried out at the Department of Medicine, Combined Military Hospital (CMH), Multan, Pakistan from February 2024 to July 2024 over a period of 6 months after taking approval from the Ethical Review Board of the hospital vide ERC no: 132/2023, dated: 12th December 2023.

The sample size was calculated with alpha equals t0 5% (two-sided), power of 90%, p1 (presence of fQRS in the CTD patients) of 55% p2 (presence of fQRS in the normal population) at 10%.[9] Estimated sample size: n1 = 21, n2 = 21.

A total of 30 patients aged 18 years or above diagnosed with various CTD (including SLE, RA, SSc, Sjogren's syndrome, polymyositis, and dermatomyositis), were recruited in the CTD group from the outpatient department through consecutive sampling.

Another 30 individuals aged 18 years or above without any known CTD or significant comorbidities were selected for the Control group from the general population present in the outpatient department. These individuals were matched with the CTD group

based on age, gender, and other relevant demographic factors.

Informed consent was received with a signature from each participant before their inclusion in this research.

The diagnosis of CTD was made based on established clinical criteria of ACR/EULAR guidelines [10]

Patients with a history of ischemic heart disease (IHD), cardiomyopathy, congenital heart disease, or other significant cardiac conditions that could independently contribute to the presence of fQRS were excluded from the study. Additionally, patients with an existing pacemaker or implantable cardioverter-defibrillator, as well as those with poor-quality ECG recordings, were also excluded.

All the demographics and clinical history, including age, gender, type of CTD, duration of disease, and other relevant details, were recorded for participants of both the groups on a predesigned proforma.

A standard 12-lead ECG was performed for each participant at rest, using a calibrated ECG machine, and was then analyzed by a consultant cardiologist. Incidents of fQRS were recorded in each group, where fQRS was defined as the presence of an additional R' wave or notching in the R or S wave within a narrow QRS complex in at least two contiguous leads.

The primary outcome of the study was to compare the incidence of fQRS in ECGs in patients with CTD with that of healthy group.

Data was analyzed using SPSS version 25. Mean ± SD was computed for continuous variables, while frequencies and percentages were calculated for categorical variables. Incidences of fQRS were compared between the two groups by applying the Chi-square test, keeping $P<0.05$ as significant. Results were stratified within the CTD group, by age, gender, and disease duration. Independent *t*-tests were used to analyze differences in incidence rates in continuous variables, while the *Chi*-square test was applied for categorical variables, with $P<0.05$ considered significant for all analyses.

Results

The mean age of study participants was 41.88±8.7 with an age range of 27-60 years. The female patients were 70% of the overall study population, while male patients were 30%. The group-wise details of demographics and medical history are shared in table-1.

The details of clinical findings in the CTD group regarding the disease showed that most of the patients were suffering from RA, followed by SLE, SSc, Sjogren's syndrome, Dermatomyositis, and Polymyositis, respectively. Details regarding the type of CTD, duration of the disease, and the organs involved are shown in table-2.

The results of the primary outcomes of the study showed that fQRS was present in significantly higher number of patients (56.66%) in CTD group compared to the Control Group (6.66%) as shown in table-3.

The stratification of the incidences of fQRS with the clinical variables in the CTD group established its association with the age of the patients and duration of the disease. However, no association was established with the gender, as shown in table-4 and 5.

Table-1: Demographics and medical history (n=60)

Demographics and medical history		CTD Group (n=30)	Control Group (n=30)
Age (Mean±SD) years		42.7 ±8.15	41.07±9.28
Gender	Male n (%)	10 (33.33)	20 (66.66)
	Female n (%)	8 (26.66)	22 (73.33)
BMI (Mean±SD)		26.03±3.19	25.66±3.03
Hypertension n (%)		4 (13.33)	2 (6.66)
Diabetes n (%)		3 (10)	2 (6.66)
Smoking n (%)		3 (10)	4 (6.66)

Table-2: Clinical findings in the CTD group (n=30)		
Type of CTD	RA n (%)	10 (33.33)
	SLE n (%)	9 (30)
	SSC n (%)	5 (16.66)
	Dermatomyositis n (%)	3 (10)
	Sjögren's syndrome n (%)	2 (6.66)
	Polymyositis n (%)	1 (3.33)
Duration of CTD	≤5 year n (%)	19 (63.33)
	>5 year n (%)	11 (36.66)
Major organs involved	Joints n (%)	9 (30)
	Kidney n (%)	5 (16.66)
	Heart n (%)	5 (16.66)
	Lungs n (%)	4 (13.33)
	Muscles n (%)	3 (10)
	Skin n (%)	2 (6.66)
	Salivary glands n (%)	2 (6.66)

Table-3: Incidence of fQRS (n=60)

Incidence of fQRS	CTD Group (n=30)	Control Group (n=30)	*Chi*-square value/df*	*P*-value
Yes n (%)	17 (56.66)	2 (6.66)	17.33/1	<0.0001
No n (%)	13 (43.33)	28 (93.33)		

*Degree of freedom**

Table-4: Stratifications of the incidence of fQRS with respect to age and duration of disease (n=30)

Continues variables	fQRS Present (n=17)	fQRS absent (n=13)	*t*-value/ df*	*P*-value
Age (Mean±SD) years	45.59±7.67	38.92±7.4	2.4/28	0.024
Duration of disease (Mean±SD) years	6.24±3.07	4.08±2.47	2.07/28	0.048

*Degree of freedom**

Table-5: Stratifications of the incidence of fQRS with respect to gender (n=30)

Categorical Variables		fQRS Present (n=17)	fQRS absent (n=13)	*Chi*-square value/df*	*P*-value
Gender	Male n (%)	6 (35.3)	4 (30.8)	0.068/1	0.79
	Female n (%)	11 (64.7)	9 (69.2)		

Discussion

The mean age of participants in our study was 41.88±8.7 with an age range of 27-60 years. The female patients were 70% of the overall study population, while male patients were 30%. The details of clinical findings in the CTD group regarding the disease showed that most of the patients were suffering from RA, followed by SLE, SSc, Sjogren's syndrome, dermatomyositis, and polymyositis, respectively. The results of primary outcomes of the study showed that a significantly higher number of patients had fragmented QRS complex in the CTD group compared to the Control group (56.66% vs 6.66%, respectively, *P*<0.0001). The stratification of the incidences with the clinical variables in the CTD group established its significant association with age (*P*=0.024) and duration of the disease (*P*=0.048); however, no association was established with gender (*P*=0.079).

The incidence of fQRS has been discussed in various studies related to different individual CTDs.

However, these results in a group of patients with diverse types of CTD are sparse. In view of following discussions, the results of key studies exploring the connection between CTDs and fQRS can be compared with our findings.

A pilot study conducted by Kadi et al. determined the frequency of fQRS in ECG in RA patients without CV disease and compared it with a control group.[11] The results showed 37.5% incidence of fQRS in patients with CTD, while this incidence was 5.7% in the control group (P<0.001).[11] A significant association was also established between the duration of disease and the frequency of fQRS (P=0.004).[11] Bayar N. investigated the incidence of fQRS in ECG in patients diagnosed with SSc. The results showed that fQRS was present in 55% of the patients with SSc, which was significantly higher than the 10% incidence in the normal population (P<0.001).[9] Hosonuma M. et al. studied the association between SLE and the prevalence of fQRS and reported the incidence to be as high as 59.1%.[12] The study thereby concluded that fQRS is a good marker of SLE and can predict future cardiac events in these patients.[12] Tomicka P. et al. determined the frequency of fQRS in ECG in patients suffering from CTD, including SSc and SLE.[13] This study reported the incidence of fQRS irrespective of the type of disease, as fQRS was reported in 46% of patients with SSc and 38% of patients with SLE. This incident was reported in only 7.5% of the normal population evaluated in this study .[13] A recent study by Kamal DE. et al., also shared the high prevalence of fQRS in the patients suffering from SLE compared to the healty group (83% vs 20.8%, respectively, P < 0.001).[14] The study therefore established a high link between the CTD and prevalence of fQRS.[14]

Beyond establishing prevalence, researchers have also investigated the prognostic significance of fQRS in CTD patients, as understanding the clinical implications of this electrocardiographic finding is equally important. Storrer KM. et al., mentioned that the presence of fragmented QRS complexes on ECG is more frequent in patients with CTD, indicating underlying myocardial involvement.[15] This finding mentioned it as a valuable, non-invasive marker to aid in the early diagnosis and risk assessment of cardiac complications in these systemic autoimmune conditions.[15] Dai J. et al., studied the incidence of fQRS in CTD-associated pulmonary arterial hypertension (PAH) and found that 24.5% of patients had fQRS, with 17.3% in the inferior leads.[16] Further details showed that fQRS in the inferior leads was linked to worse outcomes, including higher mortality, and was associated with larger right ventricular end-diastolic volume, suggesting it as good predictor of poor prognosis in CTD patients suffering from PAH.[16] Jog NR and James JA also emphasized that autoimmune CTD like SLE, RE, SC systemic sclerosis, and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides are the biomarkers with prognostic value for diagnosis, monitoring disease activity/progression, and guiding treatment.[17] Mittal SR in his review, suggested the role of fQRS in determining the cardiac involvement in patients with CTD, including SLE, RA, and SSc. fQRS on ECG was mentioned as an indicator of higher risk of arrhythmias and sudden death, and associated with multivessel coronary disease and increased cardiac events.[18] fQRS was therefore suggested as a marker of myocardial involvement and helps to detect subclinical cardiac involvement in various systemic diseases.[18] Hence fQRS is rare in the general population but potentially more common in CTD due to inflammation and fibrosis. Given the propensity for myocardial fibrosis in these conditions fQRS can serve as a valuable non-invasive marker for cardiac complications.[19]

Guler SA. et al., mentioned that diagnosing interstitial lung disease with underlying CTD complex and often delayed.[20] An interdisciplinary approach, involving rheumatology and pulmonology, enhances early detection, accurate diagnosis, and personalized treatment, ultimately improving outcomes in patients with CTD-associated interstitial lung involvement.[20] Current guidelines, thereby, emphasize that early detection of cardiac and pulmonary manifestations in CTD is essential for timely intervention and improved long-term outcomes.[10] The use of non-invasive markers such as fragmented QRS complexes, alongside coordinated multidisciplinary care, aligns with these recommendations for comprehensive management of patients with CTD.

These results of our study and the studies discussed

above are consistent with the known pathophysiology of CTD, which often involves systemic inflammation and fibrosis, affecting multiple organs, including cardiac manifestations. Hence, our study provides a broader perspective on this phenomenon than previously available in the literature. Limitations of our study include the small sample size. Moreover, we only focused on ECG findings. Future studies that include other easy-to-investigate markers of CTD will add to this useful data.

Conclusion

This study demonstrated a significantly higher incidence of fQRS in patients with CTD compared to the normal population, supporting its potential as a useful non-invasive marker. These findings also emphasize the need for further research to evaluate the prognostic value of fQRS in CTD patients, enabling early detection and targeted interventions to enhance outcomes. A critical need is also highlighted for regular cardiac monitoring, particularly in elderly patients and those with long-standing CTD.

Acknowledgement: The services of paramedical staff in taking and maintaining the record during study period are acknowledged.

Conflict of Interest: The authors declare no conflict of interest

Grant Support and Financial Disclosure: None

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Author Contributions

HW: Conception and design of the work, writing original draft (methodology, investigation)
WHB: Writing original draft (methodology, investigation), revising, editing, and supervising for intellectual content
SB: Data acquisition, curation, and statistical analysis
ZH: Validation of data, interpretation, and write-up of results
AS: Data acquisition, curation, and statistical analysis
HZP: Validation of data, interpretation, and write-up of results