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RESEARCH ARTICLE

CAN FRONTAL QRS-T ANGLE PREDICT MORTALITY IN PATIENTS WITH SEVERE CRIMEAN-CONGO HEMORRHAGIC FEVER?

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ABSTRACT

Purpose: This study aims to determine whether frontal QRS-T (fQRS-T) angle measurements assist in predicting prognosis in severe CCHF (Crimean-Congo Hemorrhagic Fever) patients.
Material and Methods: The study was conducted with 140 intensive care patients diagnosed with CCHF between 01.01.2012 and 2022. Demographic data and length of stay were recorded. In addition, laboratory data were recorded, including hemoglobin, troponin T, C-reactive protein, lymphocyte numbers, neutrophil, and platelet. fQRS-T angles were measured on electrocardiographic (ECG) data of the patients.
Results: The mean fQRS-T angle was 53.9°±29.3° in non-survivors and 34.2°±17.3° in the survivors ($p<0.001$). Regarding non-survivors, they were older, and their hemoglobin, platelet and lymphocyte levels were lower ($p<0.001$), and their QRS durations were broader ($p=0.021$) than survivors. The fQRS-T angle cutoff value in predicting mortality was determined as 41.5°. For fQRS-T ≥41.5°, specificity was 61.1%, and sensitivity was 80.9% (area under the curve: 0.711, 95% CI: 0.624–0.798, $p<0.001$).
Conclusion: Current study's results showed the usability of the fQRS-T angle as an inexpensive, convenient, strong, and repeatable predictor to determine the prognosis of CCHF patients. A detailed electrocardiographic evaluation in the routine follow-up of high-risk CCHF patients may indicate the prognosis of the disease.

Keywords: QRS-T angle, Crimean-Congo Hemorrhagic Fever, mortality, prognosis

INTRODUCTION

Crimean-Congo Hemorrhagic Fever (CCHF) is an acute viral disease caused by the *Orthonairovirus* genus of the *Nairoviridae* virus family[1]; it has a 10-30% of fatality. Initially, CCHF was reported in the 1940s in former URSS's Crimean Peninsula. Today, it is endemic in various Eastern European, Asian, and African countries.[2] The modes of transmission include tick bites, damaging infected ticks, contacting someone with CCHF in the acute phase, or contacting viremic blood and tissues. It clinically manifests itself with fever, shock, and bleeding in severe cases.[3] Multiple organ systems are involved in the progression of CCHF, including endothelium, liver, and blood cells. Multiple organ failures involving the pulmonary system have been reported in cases when CCHF progresses fatally.[4] Furthermore, cardiac involvement indications, such as pericardial effusion, myocardial hypokinesis, and electrocardiographic abnormalities, were reported in adult patients with CCHF.[5] T-wave alterations in electrocardiogram (ECG) and branch blockages in CCHF patients have been linked to adverse outcomes.[6]

The 12-lead ECG is a low-cost and noninvasive evaluation tool for cardiovascular evaluation that can be quickly employed in regular practice. Several abnormalities on ECG can be noticed in the presence of cardiovascular disease or before the signs appear. fQRS-T angle is the

angle between ventricular repolarization & depolarization. It can be utilized to detect cardiovascular disorders and predict prognosis.[7, 8] Underlying functional or structural cardiac disorders are thought to impact ventricular repolarization and result in abnormalities in the QRS-T angle.[9] Abnormal fQRS-T angle readings are powerful and independent risk predictors regarding cardiac morbidity and mortality for various conditions, including heart failure, acute coronary syndrome, cardiomyopathies, and COVID-19.[10]

Despite its high mortality, CCHF has very few mortality-predicting indicators defined. For example, the fQRS-T angle is known to increase in several myocardium-related illnesses, but no outcomes have been reported regarding its use in CCHF patients. Therefore, this study aimed to reveal whether fQRS-T angle measures may assist in predicting prognosis in hospitalized severe CCHF patients.

MATERIAL AND METHODS

Type of Research

This study is a retrospective, single-center, descriptive study.

Population and Sample of the Research

The data of CCHF patients applied to the intensive care unit (ICU) of Sivas Cumhuriyet University's Hospital between January 2012 and January 2022 were retrospectively analyzed. Two hundred patients diagnosed with CCHF, confirmed by detecting CCHF virus-specific IgM by ELISA or CCHF virus' genomic segments by RT-PCR were scanned for the study. Sixty patients were excluded because of insufficient ECG data. One hundred and forty patients were included. All enrolled patients had been transferred from the infectious disease clinic to ICU and completed a routine ribavirin treatment (an initial loading dose of 30 mg/kg, followed by 4 x 15 mg/Kg per day for 4 days; and 3 x 7.5 mg/Kg per day for 6 days). All participants in this study had a severity grading score (SGS) ≥ 9 points when they were admitted to ICU.[11]

Data Collection

On admission to ICU, the patient's ECG (Nihon Kohden, Tokyo, Japan) was taken in the supine position, with 12 leads (standard ECG, with 25 mm/s paper speed & 10 mm/mV voltage). An expert cardiologist, blinded to patients' information, manually evaluated ECGs. The information recorded on ICU admission were: heart rhythm and rate, corrected QT interval (QTc), QRS duration, and fQRS-T angle. ST depression was defined as a downward or horizontal sloping ST segment >1mm in V1-6. Moreover, the difference between the QRS complex and T wave values was defined as the fQRS-T angle. The FQRS-T angle, QRS complex, and T wave data were taken from the ECG device's automatic report. For the angle> 180°, the fQRS-T angle was obtained as follows: (360° - |angle between anterior plane QRS axis-T axis|).[8] QT was defined as the time between the start of the QRS complex & the completion of the T wave. QTc is measured using Bazett's formula ($QTc=QT/\sqrt{R-R}$). Malignant verticular arrythmia defined as sustained ventricular tachycardia, non-sustained ventrciular tachycardia presents more than 3 beats, torsades de pointes and ventricular fibrillation.

Patients' demographic data were given with the results of standard blood testing at admission, troponin T (cTnT), C-reactive protein (CRP), and hemogram parameters. Furthermore, all patients' clinical characteristics were recorded using the patient's anamnesis or hospital medical records. Patients excluded from the study were those with known severe valvular heart disease, cancer, heart failure, electrolyte imbalances, coronary artery disease, chronic renal failure, secondary infectious disease except for CCHF, underwent chemotherapy, and radiotherapy in the last year, a hematological disease affecting the blood cell

Table 1. Baseline characteristics of study patients

	Non-survivors (n:72)	Survival (n:68)	p Value
Sex (Female) (%)	28 (38.9%)	21 (30.9%)	0.321
Age (years)	53.7±19.1	45.4±18.9	**0.011**
Hospitalization time (days)	3.8±2.9	7.8±3.3	**<0.001**
Hemoglobin (g/dl)	12.2±2.8	13.8±1.9	**<0.001**
Neutrophils (10^3/μL)	4.4 (1.2-6.1)	3.1 (1.3-4.2)	0.229
Lymphocytes (10^3/μL)	1.5 (0.7-1.9)	0.7 (0.4-0.8)	**<0.001**
Platelets (10^3/μL)	20.5±14.0	42.1±26.1	**<0.001**
C-Reactive Protein (mg/dL)	54.5 (18.9-76.7)	69.6 (23.7-85.4)	0.554
Troponin T (ng/L)	51.1 (5.2-54.4)	24.3 (5.4-20.4)	0.117
Atrial fibrillation, n (%)	7 (9.7%)	5 (7.4%)	0.843
Heart rate (beats/min)	79.9±20.2	75.5±14.1	0.139
QTc (ms)	413.5±30.0	405.7±22.9	0.087
T wave changes, n (%)	13 (18.1%)	14 (20.6%)	0.869
ST depression, n (%)	16 (22.2%)	7 (10.3%)	0.094
Frontal QRS-T Angle (°)	53.9±29.3	34.2±17.3	**<0.001**
QRS duration (ms)	88.6±11.8	84.5±8.8	**0.021**
Malignant ventricular arrhythmia, n (%)	14 (19.4%)	5 (7.4%)	0.066

QTc: corrected QT interval

count and bone marrow function, diabetes mellitus with uncontrolled blood sugar, SGS score <9. Those with pacing rhythm and complete left/right bundle branch block (QRS ≥ 120 ms) ECG findings were also excluded. Patients were followed from their admission to ICU to discharge or in-hospital death.

Evaluation of Data

Study parameters were recorded in the data collection form, and the obtained data were analyzed
using IBM SPSS version 25.0. The conformity to normal distribution was checked by histograms and the Shapiro-Wilk/Kolmogorov-Smirnov test. The variables that did not fit in normal distribution are shown as a median and interquartile range, while continuous data are shown as mean and sd. The difference between categorical variables was tested using the Chi-square test. Mann-Whitney U Test, or Independent samples t-test, was used to test the difference between the means of independent patient groups. Data found to be significant after chi-square test and independent sample t-test and data correlated with fQRS-T angle were tested by univariate COX regression analysis The risk factors of in-hospital mortality were determined using multivariate Cox regression analysis (Forward-Wald method). The cutoff value of the fQRS-T angle for the mortality prediction was determined by ROC analysis, and two groups were set. The mortality in these groups was determined by Log-rank tests and Kaplan-Meier curves. Hazard ratios of the univariate and multivariate models and their confidence intervals were reported. p ≤0.05 was taken as the significance level.

Ethical Approval

In order to carry out the study, ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Sivas Cumhuriyet University (Number: 2022-01/03, Date:13.01.2022). First-degree relatives of all participating patients gave written informed consent. The Helsinki Declaration's principles were followed in this study's design.

RESULTS

Initially, 200 ICU patients were included; 60 were excluded from the study due to insufficient ECG data. The study was performed with 140 patients, 72 of whom died in-hospital (IHM).

The participants were grouped as IHM and survivors. The mean fQRS-T angle was 53.9°±29.3° in the IHM group and 34.2°±17.3°in the survivor group. Table 1 shows their baseline demographic, electrocardiographic, clinical, and laboratory results.

The IHM group was older than survivors, hemoglobin, lymphocyte, and platelet levels were lower, and QRS durations were wider. Malignant arrhythmia was more common in the group who died in the follow-up (%19.4 vs. %7.4).

Age, lymphocyte, hemoglobin, platelet levels, and fQRS-T angle values were found as possible predictors of mortality from the univariate logistic regression analysis. Regarding multivariate logistic regression analysis, hemoglobin (OR, 0.897; 95% CI, 0.816–0.987; p = 0.025), lymphocyte (OR, 1.722; 95% CI, 1.429-2.077; p <0.001), platelet (OR, 0.967; 95% CI, 0.950–0.984; p<0.001) and fQRS-T angle (OR, 1.127; 95% CI, 1.043–1.218; p =0.003) were independent predictors of mortality.

Table 2 shows the logistic regression analysis results regarding mortality. The cutoff value of the fQRS-T angle for predicting mortality was determined as 41.5° by ROC analysis. For fQRS-T ≥41.5°, specificity was 61.1% and sensitivity 80.9% (Area under the Curve: 0.711, 95% CI: 0.624–0.798, p < 0.001) (Figure 1).

Moreover, the fQRS-T angle's correlation with hemoglobin & platelet levels was negative, while its correlation with age, heart rate & malignant ventricular arrhythmia was positive (Table 3).

Table 2. Univariable and multivariable Cox regression analyses for predicting mortality

Variable	Univariable			Multivariable		
	p Value	HR	(95% CI)	*p* Value	HR	(95% CI)
Hemoglobin (g/dl)	0.010	0.886	0.808-0.971	0.025	0.897	0.816-0.987
Lymphocytes (10^3/µL)	<0.001	1.880	1.582-2.234	<0.001	1.722	1.429-2.077
Platelets (10^3/µL)	<0.001	0.958	0.940-0.975	<0.001	0.967	0.950-0.984
QTc (ms)	0.062	1.008	1.000-1.016			
Frontal QRS-T Angle (°)	<0.001	1.169	1.086-1.258	0.003	1.127	1.043-1.218
Age (years)	0.031	1.014	1.001-1.026			

CI: confidence interval, HR: hazard ratio, QTc: corrected QT interval

Table 3. Pearson correlation coeffecients for frontal QRS-T angle

	Frontal QRS-T Angle (°)	*p* Value
Age (years)	0.198	0.019
Hemoglobin (g/dl)	-0.174	0.040
Platelets (10^3/µL)	-0.198	0.019
Heart rate (beats/min)	0.190	0.025
Malignant ventricular arrhythmia, n (%)	0.193	0.023

Kaplan–Meier analysis yielded diverging survival curves for the two groups (Log-rank p<0.001) (Figure 2).

DISCUSSION

This study focused on the effect of the fQRS-T angle on the prognosis of the disease in CCHF patients. Compared to patients who survived CCHF, the fQRS-T angle and QRS duration of the patients who died were considerably higher. In addition, we revealed that the QRS-T angle is an independent predictor of prognosis. This study is the first to examine how the QRS-T angle affects CCHF patients' prognoses.

The study is also valuable in terms of the patient population it includes. For instance, patients with an SGS of 9 or higher were included in the study to ensure clinical standardization. Bakır *et al*.'s earlier research on the SGS revealed its high specificity and sensitivity for clinical risk stratification and death prediction in CCHF.[11] Additionally, it has begun to be applied in subsequent CCHF studies.[12] Regarding the current study, patients with an SGS of 9 or above, i.e., patients in high risk, were included.

Regarding previous studies, age, CRP, troponin, lymphocyte count, and QRS duration are all increasing and related to mortality.[13, 14, 15] Additionally, the bradycardic course, the decrease in hemoglobin and thrombocyte values, and the T-wave changes were shown to be linked to adverse outcomes.[6, 16, 17, 18, 19] In line with the literature, the IHM group's age, and QRS duration were higher in the current study; their lymphocyte, platelet, and hemoglobin values were significantly lower than those of the survivors.[20, 21] In addition, high age and lymphocyte values and low platelet values were found to be independent mortality determinators.

A wealth of evidence demonstrates cardiovascular involvement in the disease process, even though blood cells and the liver are principally affected during CCHF. The progression of CCHF has a predictive significance for indicators such as serum troponin T and BNP, which are objective markers of myocardial dysfunction and damage. Engin *et al*. discovered that fatal CCHF patients had a more severe decline in LVEF than non-fatal patients.[5] It is inevitable that observing ECG abnormalities in a patient group where cardiac involvement is crucial. In this study, the fQRS-T angle, which can indicate myocardial dysfunction, significantly increased among the non-survivors, and increased fQRS-T angle was an independent determinant of mortality. The QRS-T angle, defined as ventricular depolarization & repolarization, is a reliable and easy-to-measure parameter affected by cardiovascular diseases. Two different methods can be employed to measure the QRS-T angle[8]; spatial and frontal QRS-T. Measuring spatial QRS-T angle is relatively challenging and complicated, requiring 3-D images and advanced computer programs.[22] fQRS-T angle, on the other hand, is simple to measure through ECG devices' automatic report and exhibits similar results to spatial QRS-T angle in risk analysis.[23] Regarding the fQRS-T angle, the typical upper limit varies, but the accepted range is between 45° and 50°. Many observational studies conducted in the last decade associated the QRS-T angle with sudden cardiac death and other fatal and morbid outcomes.[24] A wide QRS-T angle indicates an abnormality in ventricular repolarization. Regarding the prediction of cardiac morbidity and mortality, it is a more powerful and independent risk indicator than other traditional cardiovascular risk factors and electrocardiographic risk indicators, such as QT length.[25] As the patients were split into two with the cutoff value of 41.5°, the survival rates were statistically higher in the group with fQRS-T<41.5°.

The relationship between depolarization and repolarization abnormalities, sudden death, and ventricular arrhythmia was shown in numerous studies. For example, Zampa *et al*. showed the correlation between the QRS-T angle and the development of ventricular arrhythmia in patients with cardiac involvement due to Chagas disease.[26] The current study found that the development of malignant ventricular arrhythmias such as VT and VF was significantly higher in the HIM group. In addition, QRS-T angle and malign

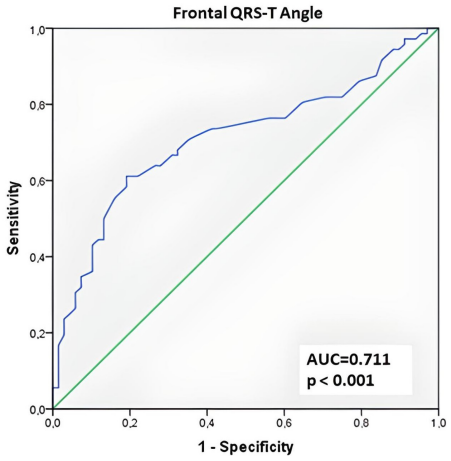

Figure 1. ROC curve of frontal QRS-T angle

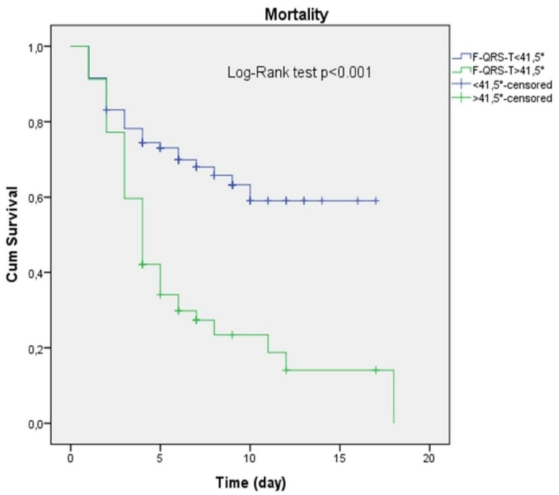

Figure 2. Log-Rank graph showing the relationship between frontal QRS-T angle>41.5° and mortality

ventricular arrhythmia development were positively correlated, consistent with the literature.

In many viral diseases, particularly *Coxsackie A and B* viruses and adenovirus, myocarditis and cardiomyopathy courses are observed.[27] It is well recognized that both immunological and direct viral cytotoxic mechanisms contribute to myocardial impaction. Focal necrosis develops in myocytes with a direct cytotoxic effect. Indirect effects can occur due to the harmful effects of natural killer cells, T lymphocytes, and cytokines (interleukin (IL)-1b, TNF-a, interferon-g, and IL-10) on myocardial functions. It has been shown that hemorrhagic fever viruses might cause heart involvement.[28] Typical myocarditis images were reported in a Hantavirus-related (which belongs to the same family called Bunyaviridae as the CCHF virus) disease.[29] Gulhan *et al.* have published case reports demonstrating the development of myocarditis in CCHF.[30] Although Yılmaz et al. have demonstrated cardiac involvement in CCHF, the pathogenesis of CCHF and cardiac involvement are not adequately explained in the current literature.[6] In this study, cardiac involvement-related indicators such as troponin, T wave alterations, and ST segment depression were analyzed, and the differences between groups were insignificant. It may be due to including patients at an advanced stage and requiring intensive care. Therefore, further investigations are required to demonstrate the cardiac involvement and, in particular, the etiology of cardiac damage in CCHF patients. Although this study has noteworthy findings, its primary limitations are the small sample size, being single-center, and the retrospective approach. The patient's cardiac function was not tested by echocardiography. Therefore, it was impossible to analyze the association between the fQRS-T angle and echocardiographic parameters. Another limitation is the inclusion of only CCHF patients who require intensive care. In addition, patients were evaluated only for IHM, and no information on long-term surveillance was available.

CONCLUSION

The current study's findings showed that the fQRS-T angle could be used to determine the prognosis of CCHF patients as a new, inexpensive, convenient, reproducible, and powerful predictor. Further studies with larger sample sizes are required to confirm these results and better explain the relationship between the fQRS-T angle and CCHF. It is thought that detailed electrocardiographic evaluation in the routine follow-up of high-risk CCHF patients may be beneficial for the prognosis of the disease.

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Conflict of interests: The authors declare that they have no competing interest.

Ethical approval: Ethical committee approval was received from the Ethics Committee of Sivas Cumhuriyet University, (Approval date: 13.01.2022, No: 01/03). The study complied with the Declaration of Helsinki

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