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Research Article | Araştırma Makalesi

FRAGMENTED QRS PATTERN PREDICTS POOR PROGNOSIS IN SEPSIS AND SEPTIC SHOCK

FRAGMENTE QRS PATERNİ SEPSİS VE SEPTİK ŞOKTA KÖTÜ PROGNOZU ÖNGÖRÜR

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ABSTRACT

Objective: Myocardial dysfunction due to sepsis is a clinical condition associated with a high rate of mortality. Fragmented QRS (fQRS) is a marker that is associated with the function of the myocardium. This study aimed to determine whether fQRS patterns were associated with short-term overall survival (OS).

Methods: 76 patients with sepsis and 68 patients with septic shock were included in the study. SOFA score and APACHE II score were calculated, and the fQRS pattern has been assessed.

Results: In the septic shock group, APACHE II score, SOFA score and mortality were significantly higher [38 (%50) vs 45 (%65), respectively; p<0.01]. Duration of mechanical ventilation, the fQRS pattern, and hospitalization time predicted the mortality. The fQRS pattern's presence was linked to a decreased short-term survival in both groups

Conclusion: fQRS pattern and mortality were significantly higher especially septic shocks. However, in both groups, the presence of the fQRS has been found to have a correlation with mortality and independently predicted worse OS. Thus, we propose that the fQRS pattern could serve as a novel prognostic indicator for septic patients.

Keywords: Sepsis, septic shock, electrocardiography, fragmented QRS

ÖZ

Amaç: Sepsise bağlı miyokardiyal disfonksiyon, yüksek mortalite oranı ile ilişkili klinik bir durumdur. Parçalanmış QRS (fQRS) miyokardın fonksiyonu ile ilişkili bir belirteçtir. Bu çalışmanın amacı fQRS paternlerinin kısa dönem genel sağkalım (OS) ile ilişkili olup olmadığını belirlemektir.

Yöntem: Çalışmaya 76 sepsis ve 68 septik şok hastası dahil edildi. SOFA skoru ve APACHE II skoru hesaplandı ve fQRS paterni değerlendirildi.

Bulgular: Septik şok grubunda APACHE II skoru, SOFA skoru ve mortalite anlamlı olarak daha yüksekti [sırasıyla 38 (%50) vs 45 (%65); p<0,01]. Mekanik ventilasyon süresi, fQRS paterni ve hastanede yatış süresi mortaliteyi öngörmüştür. FQRS paterninin varlığı her iki grupta da kısa dönem sağkalımda azalma ile ilişkilendirilmiştir

Sonuç: fQRS paterni ve mortalite özellikle septik şoklarda anlamlı olarak daha yüksekti. Bununla birlikte, her iki grupta da fQRS varlığının mortalite ile korelasyon gösterdiği ve bağımsız olarak daha kötü OS'yi öngördüğü bulunmuştur. Bu nedenle, fQRS paterninin septik hastalar için yeni bir prognostik gösterge olabileceğini düşünüyoruz.

Anahtar Kelimeler: Sepsis, septik şok, elektrokardiyografi, fragmente QRS

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Introduction

Sepsis is a severe condition characterized by organ failure due to dysregulated immune responses to infection. Septic shock, a more complex clinical condition than sepsis, is associated with higher mortality rates. Myocardial dysfunction, a hallmark of septic patients, is a critical component of multi-organ failure.[1-4] Recent studies have reported cardiac dysfunction in septic patients.[5,6] Cardiac dysfunction has been well-documented in the literature for patients with sepsis. Studies suggest that significant changes in Purkinje fibers following myocardial ischemia or fibrosis may disrupt the QRS complex morphology, leading to fragmented QRS (fQRS) patterns.[7,8] The fQRS pattern indicates irregular ventricular activation and unsynchronized contraction caused by myocardial ischemia or myocardial scarring.[9] This marker reflects pathology arising from impaired and fibrotic electrical conduction in the myocardium.[10,11] In patients with dilated cardiomyopathy, the presence of fQRS has been associated with poor prognosis. Myocardial dysfunction is observed in more than 40% of septic cases, significantly contributing to mortality and morbidity.[12] Despite the investigation of many biomarkers, no specific marker has been identified for evaluating cardiac function in septic patients. This study aims to determine the relationship between fQRS patterns and short-term overall survival (OS) in septic patients.

Methods

Study Population

This study was conducted between 2016 and 2017 in the intensive care unit of Isparta City Hospital. Ethical committee approval and the necessary permissions were obtained prior to the commencement of the study. The study included a total of 144 patients diagnosed with sepsis and septic shock according to Sepsis-3 guidelines[1] with 76 patients diagnosed with sepsis and 68 with septic shock. Patients on medication or with electrolyte imbalances that could affect ECG results, as well as those with a history of cardiac, hematological diseases, or malignancy, were excluded. Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated within the first 24 hours.

ECG Measurements

Standard 12-lead ECGs (9022-K; Nihon Kohden Corp., Tokyo, Japan) were obtained using a filter range of 0.5-150 Hz and an AC filter of 60 Hz, with a paper speed of 25 mm/s and an amplitude of 1 mV/cm while patients were in a supine position following their diagnosis. The ECGs were interpreted by two experienced cardiologists who were blinded to the study, ensuring no significant discrepancies between the investigators. All graphs were manually scrutinized to eliminate any possible technical glitches that could have affected the accuracy of the device's readings.

Measuring QRS Fragmentation

Fragmentation was defined as having different RSR patterns with different QRS complex morphologies.[13] The presence of fQRS was identified by typical bundle branch block patterns in the absence of, or with, a normal QRS duration. A coronary pattern was defined as the presence of an RSR pattern in at least two consecutive leads corresponding to the arterial blood supply area, and/or the presence of notching in the R and S waves.

Statistical Analysis

Data were analyzed using IBM SPSS v.23.0 (IBM Corp., Armonk, NY, USA) software. Continuous variables were presented as means ± standard deviation, or medians with 25^{th}-75^{th} percentile values for normally and non-normally distributed data, respectively. Continuous variables were compared using either the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-squared test. Technical term abbreviations were explained upon their first use. Kaplan-Meier analyses were employed to generate cumulative survival curves, and the log-rank test was used to compare groups. Univariate and multivariate analyses using Cox's proportional hazards model were conducted to identify differences in survival. Overall survival was calculated from the time of diagnosis until either the date of death from any cause or the date of the final follow-up. Statistical significance was defined as a p-value less than 0.05.

Results

The baseline characteristics of the two groups are presented in Table 1. Age and gender distributions were comparable between the groups.

Clinical Features

The incidence of diabetes was significantly higher in the septic shock group (p=0.02). In addition, SOFA scores (8.5±2.5 vs. 11.0±3.3; p<0.01) and APACHE II scores (20.0±5.7 vs. 23.0±6.0, respectively; p<0.01) were significantly elevated in patients with septic shock. The need for mechanical ventilation (MV) was significantly higher in patients with septic shock compared to those with sepsis (43 [57%] vs. 59 [87%]; p<0.01). Moreover, MV duration was significantly longer in septic shock patients (11.1 [0-57] vs 17.2 [0-62] days; p<0.01]. The fQRS pattern was more common in septic shock patients (27 [36%] vs. 42 [62%], respectively; p<0.01) (Table 1).

Biochemical Analysis Findings

Except for creatinine levels, biochemical tests showed comparable results between the two groups (p=0.08) (Table 2). Additionally, serum platelet levels were significantly lower in the septic shock group (p=0.04). Serum C-reactive protein levels were remarkably higher

in the septic shock group (13.1 [4-52] vs. 17.3 [4-52] mg/L, respectively; p<0.01). More importantly, serum high-sensitivity troponin T levels tended to be higher in septic shock patients compared to sepsis patients (0.17 [0-3.04] vs. 0.40 [0-3.51], respectively; p=0.06) (Table 2). Lactate levels were significantly higher in patients with septic shock (1.88±0.98 vs. 3.04±1.60 mmol/L; p<0.01). No significant differences were observed in other blood gas parameters between the two groups (Table 2).

Table 1. Change in demographic, clinical and laboratory parameters among patients with sepsis and septic shock.

	Sepsis n= 76	Septic Shock n= 68	P value
Mean age, year	76±10	75±8	0.24
Male / Female, n/n	47/29	35/33	0.24
Hypertension, n(%)	24 (%41)	30 (%57)	0.12
Diabetes, n(%)	18 (%20)	41 (%40)	**0.02**
Mechanical Ventilator, n(%)	43 (%56)	59 (%87)	**<0.01**
Mechanical Ventilator duration, day	11.1 (0-57)	17.2 (0-62)	**<0.01**
Hospitalized time, day	20 (5-61)	22 (5-62)	0.43
SOFA score, n	8.5±2.5	11±3.3	**<0.01**
APACHE score, n	20±.5.7	23±6.0	**<0.01**
Atrial fibrilation, n(%)	9 (%12)	20 (%33)	**<0.01**
QRS Fragmantation, n(%)	27 (%35)	42 (%61)	**<0.01**
Mortalite, n(%)	38 (%50)	45 (%65)	**0.03**
Glucose, mg/dl	148±45	145±61	0.75
Creatinine, mg/dl	1.36 (0.3-9)	1.49 (0.2-4)	**0.08**
Sodium, mg/dl	140±5.2	141±5.5	0.46
Potassium, mg/dl	3.9±0.7	3.9±0.8	0.58
Hemoglobin, g/dl	11±2.4	10.2±2.2	0.23
Platelet, x10³/mm³	226 (42-567)	195 (42-516)	**0.04**
Eosinophyl, x103/mL	0.13 (0.01-1.11)	0.58 (0.01-15.3)	0.13
WBC, x103/mL	12.6±6	13.1±6	0.62
C-Reactive Protein, mg/L	13.1 (4-52)	17.3 (4-52)	**<0.01**
Procalsitonin, ng/ml	4,86 (0,03-68,2)	6,71 (0,11-94,1)	0,36
Hs TnT, pg/dl	0.17 (0-3.04)	0.40 (0-3.51)	**0.06**
Lactate, mmol/L	1.88±0.98	3.04±1.60	**<0.01**

APACHE: Acute Physiology and Chronic Health Evaluation, **Hs TnT:** High Sensitive Troponin T, **SOFA:** Sequential Organ Failure Assessment Score, **WBC:** White Blood Cells.

Table 2. Results of Univariate and Multivariate Cox's Proportional Hazard Models Regarding OS.

Characteristics	Univariate Analysis		*Multivariate Analysis*	
	OS HR (95% CI)	P Value	*OS HR (95% CI)*	*P Value*
MV	0.120 (0.029-0.492)	<0.001	0.005 (0.001-0.026)	<0.001
MV duration	0.964 (0.949-0.981)	<0.001	0.849 (0.802-0.877)	<0.001
SOFA score	1.070 (1.002-1.147)	0.03		
APACHE score	1.046 (1.010-1.084)	0.01		
WBC	1.080 (1.040-1.122)	<0.001	1.043 (0.994-1.094)	0.088
Eosinophil count	1.67 (1.07-2.67)	<0.001	0.154 (0.021-1.127)	0.065
QRS Fragmantation	0.360 (0.216-0.601)	<0.001	0.228 (0.123-0.421)	<0.001

APACHE: Acute Physiology and Chronic Health Evaluation, **MV:** mechanical Ventilator **NLR**: neutrophil/lymphocyte ratio **SOFA:** Sequential Organ Failure Assessment Score. **WBC**: White Blood Cell.

Survival and Prognostic Factors

At the final follow-up, 85 patients (59%) had died. The mean survival time for all patients was 20.9 (range: 5 to 62) days, with a mean survival time of 23.2 (range: 5 to 62) days for patients who died. Mortality was significantly higher in septic shock patients compared to sepsis patients (38 [50%] vs. 45 [66%], respectively; p=0.03) (Table 1). However, OS was similar between sepsis and septic shock patients (31.3 vs. 27.4 days; HR: 1.23, 95% CI: 0.80-1.88, p=0.34). Additionally, OS was significantly

shorter in patients with fQRS compared to those without (45.5 [35.3-55.7] vs. 40.1 [32.0-48.3] days; p<0.001) (Figure 1).

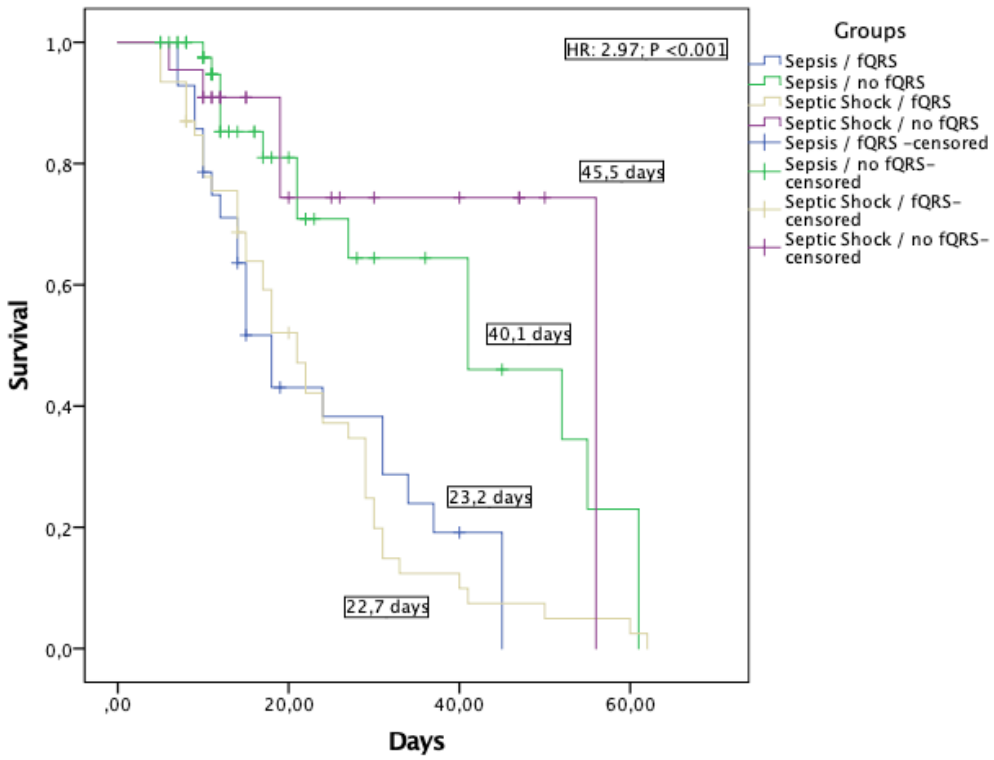

Figure 1. Survival analysis. Kaplan-Meier curves reflecting the difference in survival rates between sepsis and septic shock patients with or without fQRS.

Prognostic Analysis

Prognostic factors and the presence of fQRS patterns were initially evaluated through univariate analysis. MV, MV duration, SOFA score, APACHE II score, white blood cell count, eosinophil count, and the presence of fQRS were significantly associated with OS. Subsequently, all significant prognostic factors and the presence of fQRS were assessed via multivariate analysis using Cox's proportional hazards model. The presence of fQRS (HR: 0.228, 95% CI: 0.123-0.421, p<0.001), the need for MV (HR: 0.005, 95% CI: 0.001-0.026, p<0.001), and MV duration (HR: 0.849, 95% CI: 0.802-0.877, p<0.001) independently predicted worse OS. Detailed results of univariate and multivariate survival analyses are presented in Table 3.

Table 3. Results of Univariate and Multivariate Cox's Proportional Hazard Models Regarding OS.

	Univariate Analysis		***Multivariate Analysis***	
Characteristics	***OS HR (95% CI)***	**P Value**	***OS HR (95% CI)***	***P Value***
MV	0.120 (0.029-0.492)	<0.001	0.005 (0.001-0.026)	<0.001
MV duration	0.964 (0.949-0.981)	<0.001	0.849 (0.802-0.877)	<0.001
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APACHE: Acute Physiology and Chronic Health Evaluation, **MV**: mechanical Ventilator **NLR**: neutrophil/lymphocyte ratio **SOFA:** Sequential Organ Failure Assessment Score. **WBC:** White Blood Cell.

Discussion

This study aimed to investigate the association between the presence of fQRS patterns and short-term survival among sepsis and septic shock patients receiving intensive care. Our findings revealed a significantly higher prevalence of fQRS patterns and mortality among patients with septic shock, correlating with shorter survival times. Importantly, the need for MV, MV

duration, and the presence of fQRS patterns independently predicted worse OS in septic patients.

The APACHE II and SOFA scoring systems are standard tools in the assessment of septic patients, where elevated SOFA scores have been consistently linked to increased mortality risks.[14,15] In our cohort, the SOFA and APACHE II scores were notably higher among septic shock patients. Subgroup analyses further underscored the association between higher SOFA scores and increased mortality in patients with septic shock

The APACHE II and SOFA scoring systems are routinely used in the assessment of septic patients, where elevated SOFA scores have been consistently linked to increased mortality risks.[14,15] In our study, the SOFA and APACHE II scores were significantly higher among septic shock patients. Subgroup analyses further underscored the association between higher SOFA scores and increased mortality in patients with septic shock.

Recent literature has documented various forms of cardiac dysfunction in septic patients, including impaired contractile function, diastolic dysfunction, reduced cardiac index, and ejection fraction.[5,6] In particular, patients with septic shock frequently exhibit not only vasoplegia but also myocardial depression.[16] A post-mortem study has additionally identified myocardial injury in a significant proportion of septic shock patients.[17] In the current study, levels of serum cardiac high-sensitive troponin T were observed to be higher in patients with septic shock compared to those with sepsis. Thus, consistent with prior research, our findings suggest that myocardial dysfunction is prevalent among patients with septic shock.

Fragmented QRS patterns in patients with coronary artery disease are associated with myocardial damage and increased risk of adverse cardiac events. Moreover, studies have consistently linked fQRS patterns to elevated rates of ventricular arrhythmias, sudden cardiac death, and recurrent cardiac events in both ischemic and non-ischemic cardiomyopathy.[9-11, 18-20] Mahenthiran et al. argued that the presence of fQRS patterns may be an indicator of myocardial perfusion in coronary artery disease.[21]. In patients with hypertension, fQRS patterns have been shown to be a predictor of major adverse cardiovascular and cerebrovascular events.[22,23] Furthermore, fQRS patterns have been observed more frequently in patients suspected of cardiac involvement due to COVID-19 and are associated with increased mortality.[24]

To the best of our knowledge, there have been no previous studies investigating fQRS patterns in patients with sepsis or septic shock. In our study, although there was no significant difference in survival rates between the groups, we observed significantly higher incidences of fQRS patterns and mortality in the septic shock group. More importantly, the presence of fQRS patterns, along with the requirement for MV and MV duration, independently predicted worse OS in sepsis and septic shock patients. These findings suggest that fQRS patterns may serve as a novel prognostic marker in these patient populations.

Several limitations of our study should be acknowledged. First, the relatively small sample size due to stringent exclusion criteria limited our statistical power to detect small differences. Second, the intensive care unit-based follow-up may not capture longer-term patient outcomes. Finally, echocardiography was not utilized to assess left ventricular parameters related to myocardial scar and ischemia.

Conclusion

The current investigation identified a significant association between mortality rates and the presence of fQRS patterns, particularly in patients with septic shock. While survival rates did not vary significantly between the groups, the presence of fQRS independently predicted poorer OS in both cohorts. In conclusion, the fQRS pattern emerges as a potential novel prognostic marker for patients with sepsis or septic shock.

Description

This study was presented orally at the "23. International Intensive Care Symposium" (19-22 May 2021, Online).

Compliance with Ethical Standards

The study was approved by the Suleyman Demirel University Clinical Research Ethics Committee (21.09.2023/181).

Conflict of Interest

The authors disclose that they have no conflict of interest to declare

Author Contribution

PK: Concept; OP, YK: Data Collection and/or Processing; PK: Analysis and/or Interpretation; OP, YK, MK: Literature Review; PK, MK: Writing the Article.

Financial Disclosure

None of the authors of this manuscript had any financial relationships with other individuals or organizations.

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