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The Association of Fragmented QRS with Outcomes in Elderly Medical ICU Patients

Kamil INCI[1], Timor OMAR[2], Mustafa DILEK[3], Soner KINA[3], Zeynep BINICI CELIK[3], Doğan ILIS[2]

[1]Harakani State Hospital, Department of Intensive Care Unit, Kars, Turkey

[2]Harakani State Hospital, Department of Cardiology, Kars, Turkey

[3]Harakani State Hospital, Department of Anesthesiology, Kars, Turkey

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Corresponding Author: Kamil Inci
E mail: kamilinci@gmail.com

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ABSTRACT

Objective: The study was conducted to assess the relationship between QRS fragmentation identified by a 12-lead electrocardiogram and outcomes in elderly medical intensive care unit (ICU) patients.

Methods: The patients 65 years and older were retrospectively investigated. The patients were divided into two groups according to the presence of QRS fragmentation (fQRS). Findings were compared between two groups. In addition, ICU survivors and non-survivors were compared to identify the factors affecting ICU mortality.

Results: fQRS presence was more frequent in patients with underlying hypertension and coronary artery disease (60% vs 27%, p=0.01, and 29% vs 7%, p=0.05, respectively). Patients with fQRS had higher APACHE-II scores (26.3±8 vs 22.5±7.3, p=0.01). C-reactive protein (CRP) and procalcitonin levels were higher in patients with fQRS (100[57–220] vs 25[12–54] and 2[0.5–4.75] vs 0.2[0.7–1], respectively, p<0.01). QRS fragmentation was more frequent in ICU non-survivors than survivors (22(61%) vs 13(22%), p<0.01). ICU non-survivors had higher APACHE-II and SOFA scores than survivors (29.9±6.6 vs 0.2±5.9 and 10[7–16] vs 6[3–9], respectively, p<0.01). Requirement of invasive mechanical ventilation, APACHE-II, and SOFA Score on ICU admission were independently associated with ICU mortality (OR (95%CI): 22(2.7–147), p=0.01 and 1.28(1.04–1.59), p=0.02 and 1.10(1.01–1.19), p=0.03, respectively).

Conclusion: The fQRS has a significant potential to be a prognostic marker in specific non-cardiac ICU patient populations.

Keywords: fragmented QRS, intensive care unit, elderly, outcome

Introduction

Fragmented QRS (fQRS) is identified by a 12-lead electrocardiogram (ECG) as a result of an intraventricular conduction defect (1). The fQRS is a convenient marker of myocardial scar (1). fQRS can be defined as additional R' waves or a notch in the nadir of the R or S wave in 2 contiguous leads corresponding to a coronary territory in a 12-lead ECG (2). Data suggests that fQRS can predict cardiac events and mortality in various heart diseases (1). It is related to various cardiac conditions like coronary artery disease (CAD), cardiomyopathies, valvular heart disease, aortic dissection, and pulmonary embolism (1,2). Additionally, literature on fQRS has evolved, with non-cardiac conditions like chronic kidney disease, obstructive sleep apnea, chronic liver disease, radiotherapy in malignancies, and autoimmune disorders in the last decade (3-5).

As a predictor of mortality and cardiac events in coronary artery disease (CAD) patients, fQRS is well-studied in cardiac ICU patients (1). On the contrary, fQRS is not routinely used as a prognostic marker for non-cardiac ICUs. Thus, there needs to be more data regarding the place of fQRS in this population. In particular, fQRS complexes have gained more interest due to their potential implications on ICU outcomes in patients with novel coronavirus disease 2019 (COVID-19) after the pandemic. The interest is apparent given the association of COVID-19 with myocardial injury and arrhythmic complications (6). Studies indicate that fQRS is associated with higher all-cause mortality in patients with severe COVID-19 (7). Additionally, studies suggest fQRS can help identify patients with worse clinical outcomes admitted for severe COVID-19 infection (8). Unfortunately, the relationship between fQRS as a prognostic marker in non-cardiac ICUs is limited to this patient population. Recognizing the association between fQRS and

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outcomes in critically ill patients may contribute to developing risk stratification tools and enhancing prognostic accuracy. Additionally, the underlying comorbidities that may cause fQRS are expected to increase with age. Moreover, this effect's clinical significance is unclear in elderly critically ill patients. Thus, we conducted this study to assess the relationship between fQRS and outcomes in elderly medical ICU patients.

Methods

The study was designed retrospectively at Harakani State Hospital, Kars, Turkey Hospital, Turkey. The research protocol complied with the Declaration of Helsinki and was approved by Local Ethics Committee (28.12.2021-11). Consecutive 95 elderly patients (≥65 years old) meeting inclusion criteria admitted to our 19-bed tertiary ICU between October 2020 and October 2021 were included in the data analysis.

The patients 65 years and older were retrospectively investigated. Patients younger than 65, patients diagnosed with acute coronary syndrome or severe valvular heart disease, patients with cardiac implantable electronic devices, patients with a prosthetic valve, patients diagnosed with COVID-19 infection, and surgical ICU patients were excluded.

Demographic and laboratory data were collected from electronic hospital records and medical archives. Age, gender, Glasgow coma scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, Sequential Organ Failure Assessment (SOFA) score, need and type of mechanical ventilation support, ICU admission diagnosis, comorbidities, interventions performed in the ICU, ICU follow-up and mortality data were recorded. APACHE II and SOFA scores were calculated within 24 hours of ICU admission. Sepsis diagnosis was based on the current literature suggestions (9). The ECG parameters are routinely recorded for all patients at the first 24 hours of ICU admission. The ECG recording device was MAC 2000, GE Medical Systems Information Technologies, Inc., Wisconsin, USA. A cardiologist interpreted the ECG parameters.

The patients were divided into two groups according to the presence of fQRS. Findings were compared between two groups. In addition, ICU survivors and non-survivors were compared to identify the factors affecting ICU mortality. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 22.0. Variables were reported as medians [interquartile ranges] or frequencies and percentages according to the distribution of the data. Mann-Whitney U test was used to compare the medians of continuous variables, and $\chi 2$ (chi-squared) test was used to compare categorical variables. Logistic regression analysis was used to determine independent risk factors for ICU mortality. P values lower than 0.05 were considered statistically significant.

Results

Baseline characteristics and ICU follow-up data of the patients and comparison according to the presence of QRS fragmentation are given in Table 1 and Table 2. The percentage rate of fQRS was

Table 1. Baseline Characteristics and Comparison According to Presence of QRS Fragmentation in Elderly Medical ICU Patients

	All patients n=95	Patients with QRS fragmentation n=35 (%37)	Patients with non-fragmented QRS n=60 (%63)	p value
Age	76[69–81]	74[66–85]	77[71–81]	0.17
Female Sex	40(42%)	15(43%)	25(42%)	0.61
APACHE-II Score	24±7.8	26.3±8	22.5±7.3	0.01
SOFA Score	7[4–9]	8[4–15]	8[4–9]	0.35
Glasgow Coma Scale	12[9–15]	11[8–15]	13[9–15]	0.48
Comorbidities				
Hypertension	37(39%)	21(60%)	16(27%)	0.01
COPD/Asthma	30(32%)	13(37%)	17(27%)	0.26
Diabetes Mellitus	25(26%)	12(34%)	13(20%)	0.13
Cerebrovascular Disease	20(21%)	8(23%)	12(20%)	0.46
Malignancies	15(16%)	6(17%)	9(15%)	0.49
Coronary Artery Disease	14(15%)	10(29%)	4(7%)	0.05
Chronic Kidney Disease	4(4.2%)	1(3%)	3(5%)	0.35
Liver Failure	4(4.2%)	1(3%)	3(5%)	0.50
Causes of ICU Admission				
Respiratory Failure	66(70%)	24(69%)	42(70%)	0.53
Sepsis	57(60%)	19(54%)	38(63%)	0.21
Hypervolemia	23(24%)	8(23%)	15(25%)	0.51
Neurologic	15(16%)	6(17%)	9(15%)	0.52
Hepatobiliary	8(8.4%)	2(6%)	6(10%)	0.37
ECG Parameters				
Heart Rate (bpm)	99[69–112]	102[85–114]	99[65–112]	0.29
Atrial Fibrillation	7(7%)	4(11%)	3(5%)	0.07
QRS interval, ms	93±17	100.5±17	88.6±15	<0.01
PR interval, ms	144[134–150]	142[130–146]	144[135–162]	0.74
QTc interval, ms	415[352–431]	439[398–448]	393[352–417]	<0.01
Laboratory Findings				
Hemoglobin g/dl	12.5[10.7–13.2]	13[10–14]	12.2[9.5–13.5]	0.3
Wbc mcL10^9/L	9.0[6.8–12.0]	8.0[6.9–15.0]	8.0[6.9–10.2]	0.39
Platelet mcL10^9/L	147[110–220]	145[93.5–192]	154[123–215]	0.10
CRP mg/dL	47[14–98]	89[46.5–168]	25[9–55]	<0.01
Procalcitonin ng/ml	0.5[0.09–2]	2[0.5–4]	0.2[0.07–0.9]	<0.01
Troponin-I, ng/L	14[9–41]	24[11.5–43.5]	12[8–41]	0.05
ALT U/L	36[25–56]	36[26–56]	35[24–56]	0.61
AST U/L	25[20–40]	30[20–66.5]	24[20–33]	0.15
Creatinine mg/dL	1.15±0.96	0.7[0.45–1.05]	1[0.5–1.8]	0.014
Na mmol/L	138±10.3	135.3±13.3	140.2±9.01	0.19
K mEq/L	4.2[3.8–4.8]	4.4[3.9–4.7]	4.2[3.2–4.8]	0.87
Albumin g/dL	2.9[2.5–3.2]	2.9±0.55	2.95±0.67	0.13

ICU: Intensive care unit, **n**=Number, **APACHE–II:** Acute physiology and chronic health evaluation, **SOFA:** Sequential organ failure assessment, **COPD:** Chronic obstructive pulmonary disease, **ECG:** Electrocardiogram, **Wbc:** White blood cell count, **CRP:** C-reactive protein, **ALT:** Alanine transaminase, **AST:** Aspartate aminotransferase

Table 2. Intensive care unit follow-up and outcomes according to presence of QRS fragmentation in elderly ICU patients

	Patients with QRS fragmentation n=35 (%37)	Patients with non-fragmented QRS n=60 (%63)	p value
Mechanical ventilation			
IMV	19(54%)	16(27%)	0.02
NIMV	18(51%)	22(37%)	0.13
Central venous catheterization	18(51%)	32(53%)	0.51
Arterial catheterization	15(43%)	30(50%)	0.31
Nosocomial Infection			
Respiratory tract infection	9(26%)	13(22%)	0.36
Urinary tract infection	6(17%)	9(15%)	0.52
Catheter related infection	4(11%)	10(16%)	0.35
Shock	13(37%)	17(29%)	0.25
ICU length of stay	8[4–15]	5[3–14]	0.01
ICU mortality	22(63%)	14(24%)	<0.01
Transfusion	9(26%)	23(38%)	0.15

ICU: Intensive care unit, **n**=Number, **IMV:** Invasive mechanical ventilation, **NIMV:** Non-Invasive mechanical ventilation

higher in patients with underlying hypertension and coronary artery disease (60% vs 27%, p=0.01, and 29% vs 7%, p=0.05, respectively) (Table 1). Patients with fQRS had higher APACHE-II scores (26.3±8 vs 22.5±7.3, p=0.01). The QRS and QTc intervals were more prolonged in patients with fQRS (100.5±17 vs 88.6±15 and 439[398–448] vs 393[352–417], respectively, p<0.01), (Table 1). C-reactive protein (CRP) and procalcitonin (Pct) levels were higher in patients with fQRS (100[57–220] vs 25[12–54] and 2[0.5–4.75] vs 0.2[0.7–1], respectively, p<0.01), (Table 1). Assessment of clinical and laboratory parameters among ICU survivors and non-survivors is given in Table 3. QRS fragmentation was more frequent, and QRS interval was longer in ICU non-survivors than survivors (22(61% vs 13(22%) and (102±16.6) vs 87.4±14.1, respectively, p<0.01). Intensive care unit non-survivors had higher APACHE-II and SOFA scores than survivors (29.9±6.6 vs 0.2±5.9 and 10[7–16] vs 6[3–9], respectively, p<0.01). Additionally, ICU non-survivors had higher CRP and procalcitonin levels than survivors (100[57–220] vs 25[12–54] and 2[0.5–4.75] vs 0.2[0.7–1], respectively, p<0.01). Invasive mechanical ventilation requirement and nosocomial infection were more frequent in ICU non-survivors than survivors (p<0.5). Requirement of invasive mechanical ventilation, APACHE-II, and SOFA Score on ICU admission were independently associated with ICU mortality (OR (95%CI): 22(2.7–147), p=0.01 and 1.28(1.04–1.59), p=0.02 and 1.10(1.01–1.19), p=0.03, respectively), (Table 4).

Table 3. Assessment of Clinical and Laboratory Parameters Among ICU Survivors and non-Survivors in Elderly Medical ICU Patients

	Non-Survivors n=36 (%38)	Survivors n=59 (%62)	P value
Age	76[68–81]	75[69–82]	0.33
Female sex	14(39%)	26(44%)	0.41
APACHE–II score	29.9±6.6	20.2±5.9	<0.01
SOFA score	10[7–16]	6[3–9]	<0.01
Glasgow coma scale	10[8–13]	14[10–15]	0.01
Sepsis on ICU admission	24(67%)	33(56%)	0.2
Comorbidities			
Hypertension	17(47%)	20(34%)	0.14
COPD/asthma	10(28%)	20(33%)	0.66
Diabetes mellitus	12(33%)	13(22%)	0.12
Cerebrovascular disease	10(28%)	10(17%)	0.16
Malignancies	5(14%)	10(17%)	0.46
Coronary artery disease	5(14%)	9(15%)	0.51
Chronic kidney disease	2(5.5%)	2(3.4%)	0.12
Liver failure	1(3%)	3(5%)	0.51
ECG parameters			
Atrial Fibrillation	3(8%)	4(6.4%)	0.21
Fragmented QRS	22(61%)	13(22%)	<0.01
Heart Rate (bpm)	90[59–111]	102[85–112]	0.2
QRS interval, ms	102±16.6	87.4±14.1	<0.01
PR interval, ms	144[135–173]	143[132–148]	0.5
QTc interval, ms	418[359–440]	412[352–430]	0.17
Laboratory findings			
Hemoglobin g/dl	12.3[8–13.2]	12.5[11–13.8]	0.35
Wbc mcL10^9/L	9.5[7–14.8]	7.7[6.6–10.2]	0.19
Platelet mcL10^9/L	145[85.6–182]	147[123–209]	0.20
CRP mg/dL	100[57–220]	25[12–54]	<0.01
Procalcitonin ng/ml	2[0.5–4.75]	0.2[0.7–1]	<0.01
Troponin-I, ng/L	22.5[9.25–44]	14[8.25–32.5]	0.13
ALT U/L	55[34–108]	32[24–51]	0.02
AST U/L	30[20–88]	25[19–33]	0.51
Creatinine mg/dL	0.95±0.75	1.27±1.07	0.05
Na mmol/L	137.5±11	139±9.9	0.50
K mEq/L	4.15[3.8–4.7]	4.3[3.8–4.8]	0.34
Albumin g/dL	2.9[2.6–3.1]	3[2.5–3.2]	0.31
Mechanical ventilation			
IMV	33(91%)	18(30%)	<0.01
NIMV	18(50%)	22(38%)	0.18
Central venous catheterization	24(67%)	26(44%)	0.03
Arterial catheterization	26(72%)	19(32%)	0.02
Nosocomial Infection	21(58%)	10(17%)	<0.01

ICU: Intensive care unit, **n**=Number, **APACHE-II:** Acute physiology and chronic health evaluation, **SOFA:** Sequential organ failure assessment, **COPD:** Chronic obstructive pulmonary disease, **ECG:** Electrocardiogram, **Wbc:** White blood cell count, **CRP:** C-reactive protein, **ALT:** Alanine transaminase, **AST:** Aspartate aminotransferase **IMV:** Invasive mechanical ventilation, **NIMV:** Non-Invasive mechanical ventilation

Discussion

In this study, we investigated the requirement of invasive mechanical ventilation, APACHE-II, and SOFA score as independent risk factors for ICU mortality in elderly medical ICU patients. Additionally, our study has some significant findings regarding fQRS and its association with clinical parameters in these patients. First, fQRS was more frequent in patients with hypertension and CAD history. Second, patients with fQRS had higher APACHE-II scores, and both CRP and Pct levels were higher in these patients on ICU admission. According to these data, fQRS may be related to higher levels of inflammation and a

Table 4. Independent Risk Factors for Mortality According to Multivariate Analysis in Elderly Medical ICU Patients

	Wald Score	OR (95 %CI)	p value
Invasive mechanical ventilation	8.4	22(2.7–147)	0.01
APACHE-II score on admission	5.4	1.28(1.04–1.59)	0.02
SOFA score on admission	4.9	1.10(1.01–1.19)	0.03

ICU: Intensive care unit, **n**=Number, **APACHE-II:** Acute physiology and chronic health evaluation **SOFA:** Sequential organ failure assessment

more severe course of disease. Finally, fQRS was more frequent in ICU non-survivors than survivors in elderly medical ICU patients.

There is a strong relationship between high blood pressure and cardiovascular disease (10). Thus, the prevalence of fQRS, a convenient marker of myocardial scarring, is expected to be more frequent in patients with hypertension, especially when cardiac involvement is present. In a study by Altunova et al., fQRS prevalence was 41.3% in patients with essential hypertension, which is higher than the average population (11). We also found a higher fQRS rate in hypertensive elderly medical ICU patients than in non-hypertensive ones. Our study found the rate of fQRS to be 60% in elderly medical ICU patients with hypertension, which is relatively high. This result may be related to the patient population's advanced age and disease severity. Additionally, there is comprehensive data regarding the coexistence of fQRS as an ECG finding and CAD in the literature (12,13). We similarly found a higher fQRS rate in patients with a history of CAD.

APACHE-II score is a reliable and frequently used tool for assessing patient outcomes such as morbidity and mortality, and severity of illness in the ICUs (14). On the other hand, fQRS is not a routinely used and well-defined parameter to predict outcomes in non-cardiac ICU patients. Thus, the relationship between fQRS and this prognostic scoring system and fQRS is obscure. On the other hand, sepsis and shock are well-known as essential and frequent causes of ICU admission, morbidity, and mortality (15). From a different point of view, myocardial perfusion is negatively affected in patients with septic cardiomyopathy and shock, likewise in patients with CAD (16). A study by Das et al. evaluated 471 patients referred for myocardial SPECT stress testing with CAD or who had a history of CAD or a prior myocardial infarction (17). They found that fQRS is associated with significantly greater perfusion and function abnormalities than is the Q wave, which makes fQRS an important ECG-derived parameter to predict myocardial perfusion abnormalities. Likewise, the study of Mahenthiran et al. concluded that QRS complexes are a marker of higher stress for myocardial perfusion and functional abnormalities in 501 patients with suspected CAD (18). Considering all data, two significant findings of the current study, the more frequent presence of fQRS in ICU non-survivors than survivors and patients with higher APACHE-II scores to have more frequent fQRS may both be explained by myocardial perfusion abnormalities in more severe critical illness.

Moreover, CRP and Pct are essential markers to guide the diagnosis and course of infectious diseases in ICUs. A study by Xie et al. showed that a bioscore using CRP and Pct could help identify septic patients earlier in the ICU (19). In addition to their ability to help diagnose infections, CRP and Pct have the potential to diagnose sepsis earlier as diagnostic markers. Our study found higher CRP and Pct levels in patients with fQRS. This result may be a result of organ perfusion abnormalities in sepsis, likewise the relationship between APACHE-II scores with fQRS. According to all accounts, fQRS, a predictor of mortality and cardiac events in patients with coronary artery disease, have the potential to predict morbidity and mortality in non-cardiac ICU patients. Even though fQRS is not routinely used and well defined in non-cardiac ICUs, the data obtained from the current study address a significant potential.

Nonetheless, in our study, fQRS was not more common in patients presenting with sepsis than those not presenting as a cause of ICU admission. Additionally, shock in the ICU follow-up was not more frequent in patients with fQRS on ICU admission. These findings show an inconsistency with the main findings of our study. On the other hand, considering the complexity and heterogeneity of the ICU patient population, many factors affect the course of the disease in patients with sepsis and shock. Additionally, heterogeneity in timing and treatment strategies before ICU admission may significantly affect the course of the disease, sepsis-related morbidity, and mortality. In addition, in the ICU follow-up, multiple possible scenarios may cause a hypotensive attack or the presence of shock, like pulmonary complications, adrenal failure, and hypovolemia.

In the current study, both QRS and QTc intervals were more prolonged in patients with fQRS than those with non-fragmented QRS. Given the nature of fQRS, as a result of myocardial perfusion and intraventricular conduction defects, these patients may be prone to different conduction abnormalities (1,2).

Our study has some limitations. A relatively small number of subjects for a heterogeneous population like a medical ICU and the lack of echocardiographic data are the main limitations of the current study. Additionally, we did not have ECG data of the patients before ICU admission and during ICU and hospital follow-up, which could guide us to understand whether f-QRS develops because of critical illness.

Conclusion

As a predictor of mortality and cardiac events in patients with coronary artery disease, fQRS has the potential to predict outcomes in non-cardiac elderly medical ICU patients. Even though fQRS is not routinely used and well defined in non-cardiac ICUs, the data obtained from the current study address the potential for studies in specific non-cardiac ICU patient populations.

AUTHOR CONTRIBUTIONS:

Concept: KI, TO; **Design:** KI, TO; **Supervision:** KI, MD, SK, TO, ZBC; **Fundings:** MD, SK, TO; **Data Collection and/or Processing:** KI,TO,DI; **Analysis and/or Interpretation**: KI, TO; **Literature Search:** KI; **Writing Manuscript**: KI; **Critical Review:** KI, TO.

Ethics Committee Approval: Kafkas University Medicine Faculty Ethics Committee (28.12.2021–11)

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